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Postgraduate Medicine

Volume 12 · Number 4
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OFFICIAL JOURNAL OF THE INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION

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THE 1952 Assembly *OF THE*

INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION

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CLEVELAND PUBLIC AUDITORIUM

November 10 to 13 (inclusive) 1952

DR. GEORGE CRILE, SR.

FOREWORD

DR. George Crile, Sr., would have been very much pleased and interested to help in the preparation of this issue. He was always interested in this type of clinical publication, particularly so since he felt so deeply about the influence and real good which the Interstate Postgraduate Medical Association exerts. I know how jealous he was of the programs, and how closely he watched the presentation of clinical material before the Assembly. He always liked to sit either in the back of the hall or backstage, in a position where he could better watch and hear these presentations, and mentally grade them for future reference. As the Chairman of the Program Committee, he considered it a real obligation that he have the best clinical presentations it was possible for him to arrange. He would have felt this same responsibility in aiding in the publication of this Journal, for the simple reason that it is sponsored by the Interstate Postgraduate Medical Association. Actually, Dr. Crile's two favorite meetings were the sectional meetings of the American College of Surgeons and the Interstate Postgraduate Assembly, because he believed that the former were of the most value to general surgeons, and the latter was of the most value to the physician who wanted information in all fields of medicine.

ROBERT S. DINSMORE, M.D.
Chief of Surgery, Cleveland Clinic

Chronic Pyelonephritis: An Important Cause of Hypertension

DAVID C. HUMPHREY

Cleveland Clinic and the Frank E. Bunts Educational Institute, Cleveland

Hypertension is a frequent complication of chronic pyelonephritis. Modern drug therapy can control bacterial infection of the kidney. Hypertension due to pyelonephritis should be prevented by adequate treatment of the primary infection. If hypertension does occur, it can be controlled by elimination of the renal infection.

D. C. HUMPHREY

PYELONEPHRITIS is unique among diseases of the kidney. Its natural history is known in detail, and drugs are available which will cure it or arrest its advance. Modification of the disease by specific therapy is often accompanied by amelioration of various complications. That these complications, including hypertension, are a frequent cause of disability and death has been recognized for several years. However, pyelonephritis still excites relatively little interest. The diagnosis is made infrequently, and treatment is often inadequate. These facts are in sharp contrast to those pertaining to nephrosclerosis and glomerulonephritis.

Incidence of Chronic Pyelonephritis

While it is difficult to determine the exact incidence of pyelonephritis, the disease apparently is one of the three commonest lesions of the kidney. Weiss and Parker[1] demonstrated that acute pyelonephritis is the kidney disease most generally encountered. Raaschou[2] studied 3,607 necropsy reports of patients over 10 years of age and found that 173, or 1 in 20, died of pyelonephritis. One-third of these, or one-fiftieth of the entire number examined at autopsy, were found to have pyelonephritis that was not secondary to other disease inside or outside the urinary tract. Bell,[3] on the other hand, reported only 14 cases of chronic pyelonephritis not associated with hydronephrosis in 32,360 postmortem examinations.

Incidence of Hypertension in Chronic Pyelonephritis

It is even more difficult to determine accurately how often pyelonephritis is the cause of hypertension. It is generally accepted that the two conditions are associated frequently enough to indicate that hypertension does result from chronic pyelonephritis. The various reports in the literature are summarized in Table 1. Bell's interpretation of these data differs from that of several other authors because many patients had coexisting arteriosclerosis or glomerulonephritis and because of the frequency of hypertension in the older age group. Pearman, Thompson and Allen[4] reported that the incidence of hypertension in patients with chronic pyelonephritis is no greater than in patients of comparable age with diseases not known to cause hypertension. The estimate of Weiss and Parker[5]

TABLE 1

INCIDENCE OF HYPERTENSION IN CHRONIC PYELONEPHRITIS
(SUMMARY OF REPORTS IN THE LITERATURE)

YEAR	AUTHORS	CASES STUDIED	FINDINGS
1933	Longcope and Winkenwerder[10]	9 pyelonephritis	5 hypertension
1936	Kimmelstiel and Wilson[11]	26 primary pyelonephritis	20 hypertension (16 also renal failure)
1937	Longcope[12]	22 pyelonephritis (3 also glomerulonephritis)	10 hypertension
1937	Butler[13]		15 hypertension and pyelonephritis
1939	Weiss and Parker[5]		38 malignant hypertension and pyelonephritis
1939	Crabtree and Prien[14]	30 pyelonephritis (pregnancy)	2 hypertension over 10 years later
1940	Pearman, Thompson and Allen[4]	Gallbladder disease Nodular goiter Pyelonephritis	7 per cent hypertension 10 per cent hypertension 9 per cent hypertension
1942	Bell[3]	12 pyelonephritis (1 also glomerulonephritis)	5 hypertension
1942	Boyd[15]	38 pyelonephritis	8 hypertension
1943	Mansfield, Mallory and Ellis[16]	17 pyelonephritis	8 hypertension
1948	Raaschou[2]	173 pyelonephritis (necropsy)	28 died of hypertension
1949	Davson and Platt[6]	25 pyelonephritis (necropsy)	14 hypertension (4 "malignant")

that 15 to 20 per cent of all cases of malignant hypertension are secondary to chronic pyelonephritis is usually considered high, but Davson and Platt[6] found arteriolonecrosis in 4 of 14 patients with hypertension.

Etiology of Renal Hypertension

The mechanism of the production of hypertension remains obscure in patients with renal disease although the association of renal disease and hypertension has been recognized in clinical medicine since the work of Bright over 100 years ago. Recent experiments have confirmed the role of the kidney in the production of persistent elevation of blood pressure. Goldblatt, et al.[7] (1934) partially occluded the renal artery with a clamp. Page[8] (1939) produced perinephritis by wrapping the kidney in an envelope of cellophane or with silk thread. Goldblatt attributed the elevation of blood pressure to renal ischemia. Corcoran and Page[9] studied the renal blood flow and glomerular and tubular function and concluded that experimental renal hypertension may occur in the absence of ischemia of excretory renal tissue. They observed secondary diminution of renal blood flow due to arteriolar constriction and suggested that reduction of intrarenal pulse pressure, rather than renal ischemia, might be the cause of hypertension. The details of the pressor mechanism are not established. The evidence suggests the liberation and activation of humoral agents which result in persistent hypertension.

Pathology of Chronic Pyelonephritis

It is important that the fundamental pathologic changes in chronic pyelonephritis be emphasized, not only for complete understanding of the disease but also for the rational

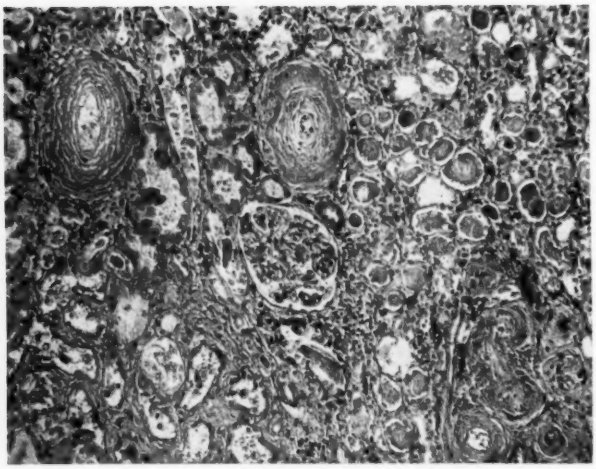

FIGURE 1. Photomicrograph (x 70) illustrating the atrophic epithelium and casts of dilated renal tubules, inflammatory cells in the increased interstitial tissue, and the vascular lesions in a patient with chronic pyelonephritis and malignant hypertension.

planning of treatment. Pyelonephritis is the result of inflammation of the interstitial tissue of the kidney and renal pelvis due to bacterial infection, with secondary changes in the blood vessels, tubules and glomeruli. The disease may be unilateral or bilateral and it may or may not be associated with lesions lower in the urinary tract. The bacteria may ascend the ureters, or travel through the perureteral lymphatics, or be deposited in the kidney by the perfusing blood.

On gross examination the kidney may be enlarged, normal in size or smaller than normal. The capsule is adherent and the surface is irregular with U-shaped scars alternating with regions composed of tubules exhibiting compensatory dilatation. There is irregular narrowing of the cortex produced by the contracted scar tissue. The walls of the pelvis are thickened.

Microscopic study of the involved regions shows the dilated tubules to be lined with flattened atrophic epithelium and to contain "colloid" casts. In addition there is periglomerular fibrosis and alterative glomerulitis,[11] as well as infiltration of the increased interstitial tissue with inflammatory cells.

Weiss and Parker[5] first emphasized the vascular lesions. These changes are more evident in the involved regions of the kidney and are infrequently found outside the kidney. When the disease is unilateral the changes are more advanced in the diseased kidney. The alterations are more pronounced when hypertension has occurred. The arteries show productive endarteritis with increased connective tissue in the intima, reduplication of the elastic membrane, and medial hypertrophy. The arterioles exhibit hyperplastic arteriosclerosis with concentric proliferation of the cells resulting in thickening of the walls. In some cases the arteriolar necrosis of malignant hypertension is seen in addition. Weiss and Parker concluded that these changes result both from the inflammatory process and from the intravascular pressure. They compared the alterations with those found in the lungs of patients with mitral stenosis[17] and differentiated them from the changes in nephrosclerosis and in disuse atrophy. The microscopic changes in the interstitial tissue, tubules and blood vessels are shown in Figure 1.

Diagnosis

The diagnosis of chronic pyelonephritis is frequently difficult and sometimes impossible. This is particularly true in the patient with renal failure and hypertension. It has been estimated, however, that the correct etiologic diagnosis can be made in 85 per cent of cases if proper care is exercised.[6] The natural history of pyelonephritis is variable, which ac-

counts for much of the difficulty in diagnosis. The disease occurs in either sex and at any age from infancy to old age. It may begin as "pyelitis" in childhood, as toxemia of pregnancy or as recurrent cystitis, cryptic anemia or unexplained fever in adults. The disease terminates usually in renal failure or in hypertension in middle or old age, and the first manifestation may be the onset of the terminal stage.

Chronic pyelonephritis may be secondary to renal lithiasis or an obstruction of urine flow due to disease of the pelvic viscera or the prostate gland. There may be recurrent episodes of typical acute pyelonephritis, or prolonged low grade illness manifested by anorexia, pallor, lethargy, obscure fever and abdominal pain. Extensive edema does not occur. Late in the course of the disease, hypertension with retinopathy may result, but cardiac enlargement and failure and cerebral vascular disease are not as common as they are in nephrosclerosis. The disease can progress in the absence of evidence of active inflammation. The possibility of pyelonephritis as a cause of illness of obscure etiology must be kept in mind and positive effort made to prove or disprove the diagnosis if greater accuracy in antemortem diagnosis is to be achieved.

Urine—Typically, examination of the urine discloses pyuria, bacilluria, moderate proteinuria and low specific gravity. Usually the organisms can be cultured and identified. Persistent hematuria is not found and casts are only moderately increased in number. However, hematuria occurs from time to time and may be massive. Bacilluria and pyuria may be intermittent and, late in the course of the disease, may be absent for long periods. The colon bacillus is the organism most often identified. Examination of the urine by the Addis technic gives maximum information with a minimum of expense and trouble.

Blood—Normocytic and normochromic anemia may be present late in the course of the disease. Elevation of the sedimentation rate and leukocytosis are found in chronic pyelonephritis only if there is an acute exacerbation and thus are of little diagnostic help.

Renal function—Tests of renal function show great variation in the same patient, depending on the degree of activity and the extent of the inflammatory lesion. In contrast to the other types of Bright's disease, in pyelonephritis remarkable improvement in renal function may occur even in patients with severe renal failure. In clinical practice a single test such as the determination of the urea clearance will give sufficient information for satisfactory evaluation of the amount of renal damage.

Pyelography—Pyelographic studies may reveal an obstructing lesion or hydronephrosis, as well as distortion of the renal pelvis and calyces. Any decrease in size of the kidney, abnormal position, or variation between the two kidneys can be visualized. Such examination also provides an estimate of renal function. An intravenous urogram should be part of the study of suspected cases of pyelonephritis. If more accurate information is needed, retrograde studies may be carried out.

Treatment

The proper treatment of pyelonephritis is extremely important because it may be effective in altering the course of a disease that often causes disability and death.

It has been shown that the primary lesion of pyelonephritis is infection of the interstitial renal tissue. Therefore the object in therapy should be the elimination of tissue infection and not just sterilization of the urine. Mandelic acid and MANDELAMINE® are ineffective because they are not active at the *p*H of the tissue fluids. The sulfonamide drugs, the antibiotics or a combination of both often result in eradication of the organisms and thus in arrest of the disease. The degree to which the function of the kidneys returns to normal depends on the amount of renal tissue destroyed.

Any lesion obstructing the flow of urine should be removed, since elimination of infection in the presence of stasis is difficult and often impossible, and recurrence of infection is frequent.

Sulfonamides—The sulfonamide drugs, alone or in combination, remain the drugs of

choice when given in sufficient dosage to maintain a plasma concentration of 10 to 12 mg. per hundred cubic centimeters.[18] They are inexpensive, relatively safe to use and effective against a wide variety of organisms. They should be given for at least one month and may be used indefinitely if necessary to control the activity of resistant organisms or to prevent recurrent infection.

Antibiotics—Many of the newer antibiotics are effective in urinary tract infections, though penicillin alone is ineffective against most of the bacteria. It is desirable to determine the sensitivity of the organism cultured from the urine to the various available antibiotics, and then to use the indicated preparation in therapeutic dosage, rather than to rely on published sensitivity studies. Streptomycin is particularly effective in vitro against several of the more resistant organisms, and the renal tissue concentration is greater than the plasma concentration. Unfortunately the organisms rapidly develop a tolerance, so that prolonged use of this drug is not indicated. The use of penicillin and streptomycin combined in a short, intensive course of treatment may be effective when other forms of treatment fail.

The initial use of antibiotics for one to two weeks, followed by one of the sulfonamide preparations for another four weeks or longer, is usually sufficient to effect a cure. It should be remembered that the infection in chronic pyelonephritis is more resistant than that found in the acute stage of the disease. Monthly urinalyses and urine cultures should be made for at least six months to determine whether the infection has been eliminated and to detect evidence of recurrence.

Summary and Conclusions

1. Chronic pyelonephritis is not an uncommon disease and hypertension is a frequent complication.

2. Since pyelonephritis is the result of bacterial infection, and since effective treatment is available, hypertension related to pyelonephritis can be prevented or controlled.

3. While the details of the complex pressor mechanism are not known, experimental evidence suggests that altered intrarenal blood flow results in the liberation and activation of humoral agents which have their effect on the smaller blood vessels.

4. The natural history of pyelonephritis is reviewed and the variability of the clinical picture emphasized.

5. The importance of prolonged intensive specific treatment based on knowledge of the pathogenesis of pyelonephritis is stressed.

REFERENCES

1. Weiss, S. and Parker, F., Jr.: Relation of pyelonephritis and other urinary tract infections to arterial hypertension. New England J. Med. 223:939 (December 12) 1940.
2. Raaschou, F.: Studies of Chronic Pyelonephritis with Special Reference to the Kidney Function. (Translated by W. E. Calvert.) Copenhagen, Ejnar Munksgaard, 1948.
3. Bell, E. T.: Exudative interstitial nephritis (pyelonephritis). Surgery 11:261 (February) 1942.
4. Pearman, R. O., Thompson, G. J. and Allen, E. V.: Urographic evidence of renal lesions in series of patients suffering from essential hypertension. Proc. Staff Meet., Mayo Clin. 15:467 (July 24) 1940.
5. Weiss, S. and Parker, F., Jr.: Pyelonephritis; its relation to vascular lesions and to arterial hypertension. Medicine 18:221 (September) 1939.
6. Davson, J., Jr. and Platt, R.: Clinical and pathological study of renal disease; diseases other than nephritis. Quart. J. Med. 19:33 (January) 1949.
7. Goldblatt, H., Lynch, J., Hanzal, R. F. and Summerville, W. W.: Studies on experimental hypertension; production of persistent elevation of systolic blood pressure by means of renal ischemia. J. Exper. Med. 59:347 (March) 1934.
8. Page, I. H.: Production of persistent arterial hypertension by cellophane perinephritis. J.A.M.A. 113:2046 (December) 1939.
9. Corcoran, A. C. and Page, I. H.: Renal blood flow in experimental renal hypertension. Am. J. Physiol. 135:361 (January) 1942.
10. Longcope, W. T. and Winkenwerder, W. L.: Clinical features of contracted kidney due to pyelonephritis. Bull. Johns Hopkins Hosp. 53:255 (November) 1933.
11. Kimmelstiel, P. and Wilson, C.: Inflammatory lesions in glomeruli in pyelonephritis in relation to hypertension and renal insufficiency. Am. J. Path. 12:99 (January) 1936.
12. Longcope, W. T.: Chronic bilateral pyelonephritis; its origin and its association with hypertension. Ann. Int. Med. 11:349 (July) 1937.
13. Butler, A. M.: Chronic pyelonephritis and arterial hypertension. J. Clin. Investigation 16:889 (November) 1937.
14. Crabtree, E. G. and Prien, E. L.: Nature of renal injury in acute and chronic colon bacillus pyelonephritis in relation to hypertension. J. Urol. 42:982 (December) 1939.
15. Boyd, W.: Changing concepts of pyelonephritis. Canad. M. A. J. 47:128 (August) 1942.
16. Mansfield, J. S., Mallory, G. K. and Ellis, L. B.: Differential diagnosis of chronic Bright's disease; clinico-pathologic correlation. New England J. Med. 229:387 (September) 1943.
17. Parker, F., Jr. and Weiss, S.: Nature and significance of structural changes in lungs in mitral stenosis. Am. J. Path. 12:573 (September) 1936.
18. Birchall, R. and Alexander, J. E.: Medical aspects of pyelonephritis. Medicine 29:1 (February) 1950.

The Diagnosis and Treatment of Hyperparathyroidism

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Hyperparathyroidism is a seldom recognized, and consequently frequently untreated, disease. This article presents an approach to its diagnosis and describes the major clinical manifestations in the three most common forms, together with the surgical aspects. It is emphasized that a low serum phosphorus and an elevated serum calcium are more significant when occurring together in hyperparathyroidism than when either condition is present alone.

R. W. SCHNEIDER

HYPERPARATHYROIDISM is a curable disease, but may be fatal when untreated. It is seldom recognized before it has caused prolonged ill health, and at times the diagnosis is first made at postmortem examination. Greater awareness of the clinical manifestations of the disorder is essential for earlier and more frequent detection. The purpose of this paper is to present an approach to the diagnosis of hyperparathyroidism with particular emphasis on the less classic and less generally appreciated features of the disease.

The original descriptions of hyperparathyroidism emphasized the high blood calcium content and the occurrence of osteitis fibrosa cystica. The frequent renal complications were not appreciated, and it was not realized that in some cases the blood phosphorus concentration is more affected than are the blood calcium levels. Furthermore, the emphasis which was placed on the skeletal changes served to direct attention from the more numerous cases in which osteitis fibrosa cystica is not present.

The variability of the clinical manifestations of hyperparathyroidism adds to the difficulty in diagnosis. At times the symptoms are so mild that their significance is entirely overlooked. Final establishment of the diagnosis depends on an indirect chemical approach. There is no direct method of assaying parathyroid hormone in the blood, and one must therefore rely on tests which indicate the metabolic changes resulting from an overproduction of the hormone. An understanding of normal and abnormal parathyroid physiology is thus a prerequisite to correct diagnosis.

Normal and Abnormal Parathyroid Physiology

Despite lack of uniform agreement on its site and mode of action, the four significant and generally accepted changes following the administration of parathyroid hormone consist of a prompt phosphate diuresis, a subsequent reduction in serum phosphorus concentration, an almost simultaneous rise in serum calcium and an eventual rise in urinary calcium excretion. This sequence was clearly shown by Albright and Ellsworth in 1929.[1] In hyperparathyroidism, where a constantly

increased excretion of parathyroid hormone presumably occurs, similar changes are expected, namely, hyperphosphaturia, hypophosphatemia, hypercalcemia and hypercalciuria, in that order.

It is to be noted that the changes in phosphorus metabolism precede alterations in calcium. This may explain those mild cases which present normal (or near normal) serum calcium and low serum phosphorus levels. Even in these mild cases, however, calcium balance may be sufficiently disturbed to lead eventually either to renal changes in the form of renal calculi or diffuse renal calcinosis with varying degrees of impairment in renal function, or to skeletal changes consisting of osteitis fibrosa, diffuse demineralization, giant cell tumor formation, deformity or fracture.

Many patients with severe hyperparathyroidism have no bone disease at all; others have no kidney defect, while some will present both. An occasional patient will have neither. In general, a diet high in calcium tends to prevent skeletal changes and to increase the frequency of renal complications, while a diet low in calcium has the reverse effect. Thus, patients with hyperparathyroidism who drink milk usually have less bone disease and more frequent stones, while those who dislike milk suffer greater skeletal and fewer renal complications.[2] Consequently no medical program has been found suitable for the management of this disease.

Symptoms and Physical Signs

The symptoms of hyperparathyroidism are exceedingly variable. There may be no symptoms whatever, or the presenting complaints may be limited either to the skeletal or to the renal manifestations of the disease. There are, however, certain symptoms which often accompany hypercalcemia. These include fatigue, muscular weakness, muscular flaccidity and reduced or absent reflexes. Constipation, anorexia, nausea and vomiting—sometimes leading to loss in weight—are sufficiently prominent as to simulate major gastrointestinal disease such as duodenal ulcer.

Those cases of hyperparathyroidism in which the gastrointestinal symptoms dominate the picture deserve further comment. They depend directly on the hypercalcemia and disappear immediately upon removal of the hyperparathyroidism. Morelle[3] in 1932 described one of the first cases of this type. In his patient the presence of pernicious vomiting suggested intestinal obstruction. The blood calcium level of 19.7 mg. per cent became normal and the vomiting ceased after the tumor was removed. Beyerinck[4] described a similar experience. Rogers,[5] Rogers, Keating, Morlock and Barker,[6] and Schneider and Robnett[7] reported patients with duodenal ulcer and hyperparathyroidism. In the latter instance the duodenal ulcer which resisted medical treatment healed after the tumor was removed (Case 2).

Acute exacerbations of hyperparathyroidism occur occasionally. Large quantities of parathyroid hormone are presumably released; a pronounced rise in serum calcium results, leading to pernicious vomiting, lethargy, calcium precipitation and secondary necrosis of the renal tubules, and death in "parathyroid crisis" ensues.

Polydipsia and polyuria may occur and be of sufficient intensity to simulate diabetes insipidus. The disease in these instances is usually associated with nephrocalcinosis, and the elimination of the hyperparathyroidism is often followed by oliguria and azotemia for a short time. Occasionally the kidney damage and azotemia persist and may prove fatal. Albright and Reifenstein[2] have suggested that the polydipsia and polyuria may act as a protection against the development of renal calculi, and point out that such patients rarely have kidney stones.

The following case is an example of hyperparathyroidism simulating diabetes insipidus.

Case 1—A 50 year old mechanic complained of extreme thirst and polyuria of three months' duration, nocturnal frequency, a 10 pound loss in weight, muscular weakness and severe constipation. There was no nausea or vomiting, no skeletal discomfort and no history of kidney stones. There was no glycosuria or hyperglycemia. Physical examination was negative. A presumptive diagnosis of diabetes insipidus was made. Roentgenograms of

the skull showed a diffuse, mottled appearance. Excretory urograms were normal. The blood calcium concentration was 13.0; total serum proteins measured 6.9; the serum phosphorus level was 2.1 and the alkaline phosphatase level 18.5 mg. per cent. A 5 gm. parathyroid tumor measuring 3.0 by 1.8 by 1 cm. in diameter was removed from the right inferior parathyroid gland. All symptoms rapidly disappeared and blood chemical findings reverted to normal; active tetany appeared as would be anticipated (see later discussion) and required treatment for a five month period.

The symptoms produced by the bone disease in hyperparathyroidism are very nonspecific. Any bone tumor which, when biopsied, is classified as a benign giant cell tumor may be due to hyperparathyroidism (Figure 1). Such a bone tumor has a special predilection for the jaw and is then called an epulis (Figure 2). Not all epulides are due to hyperparathyroidism any more than are all benign giant cell tumors. However, tumors containing giant cells may occur in hyperparathyroidism as isolated defects in the skeleton (particularly the skull) without other clinical or roentgenographic evidence of bone disease elsewhere. Barr[8,9] described such a case, while Snapper[10] referred to the occurrence of recurrent osteofibromas of the skull in one instance of hyperparathyroidism. The remainder of the skeleton was normal; hypercalcemia and hypercalciuria disappeared promptly after parathyroid surgery.

Other skeletal changes consist of spontaneous fractures, generalized long-bone tenderness, soreness in muscles, reduction in height, diffuse or localized bone pain or a feeling of insecurity when walking, particularly up or down stairs.

Roentgenologic studies of the teeth are of value in the diagnosis of hyperparathyroidism. The teeth themselves remain normal but there may be loss of calcium from the supporting lamina dura, with loosening of the teeth (Figgure 3). Sometimes the teeth fall out of their sockets. Resorption of the lamina dura is more common to hyperparathyroidism than to other diseases involving bones but is not

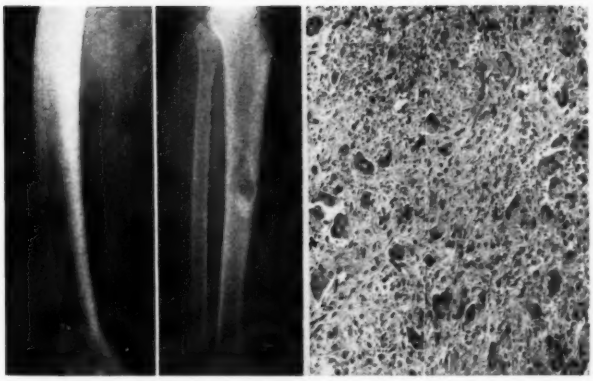


FIGURE 1. Roentgenograms demonstrating bowing of femur and cyst of tibia. Photomicrograph of biopsy specimen taken from cystic area shows typical benign giant cell tumor.

FIGURE 2. Photograph and x-ray of patient with large epulis due to hyperparathyroidism.

pathognomonic of the disease, as shown by the patient with hypernephroma reported in this paper (Case 4).

Clubbing of the fingers is a rare skeletal change seen in hyperparathyroidism. A loss of calcium from the terminal phalanges is associated with the clubbing in this disease. The roentgenographic differentiation from the more common causes of clubbing is not difficult, since such decalcification does not occur in the pulmonary osteoarthropathies.

Urinary calculi in hyperparathyroidism are among the more common manifestations of the disease. They are composed of calcium

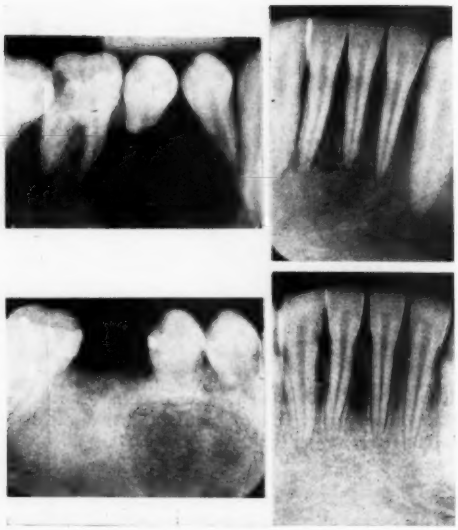


FIGURE 3. X-rays of teeth of patient with hyperparathyroidism, showing loss of lamina dura and repair after removal of tumor.

TABLE 1

LOW CALCIUM DIET FOR USE IN DIAGNOSIS OF HYPERPARATHYROIDISM

(AUB DIET AS MODIFIED BY ALBRIGHT AND REIFENSTEIN[2])

Breakfast	
Orange juice	1 small glassful
Farina or rice	½ cup after cooking
UNEEDA® biscuits	4
Bacon	3 strips, crisp
Luncheon	
Lean meat	medium serving
Potato	medium serving
White corn	½ cup
Uneeda biscuits	4
Apple sauce	½ cup
Dinner	
Chicken	medium serving
Macaroni	⅓ cup after cooking
Canned tomatoes	½ cup
Uneeda biscuits	4
Banana	1 medium

NOTE: Use margarine, sugar, salt, pepper, coffee and tea as desired in the diet. Use margarine and sugar generously to maintain weight. Eat above foods and *no other* foods each day. Some cereals and margarines are fortified with added calcium.

phosphate and calcium oxalate, but their composition may be altered by superimposed infection. Although hyperparathyroidism is an uncommon cause of kidney stones, it is estimated that among all patients with hyperparathyroidism 60 per cent will have either renal calculi or nephrocalcinosis, or both.

Hypercalciuria is almost always present in hyperparathyroidism. It is doubtful that the disease ever exists in its absence. The normal daily calcium excretion is somewhat variable, depending on intake. After four days on an Aub diet (Table 1) the normal 24 hour urinary calcium excretion is 100 to 150 mg. It is well over 200 in hyperparathyroidism, and when values less than 150 mg. per 24 hours are found the disease generally can be excluded. The many nonparathyroid causes of hypercalciuria must be reviewed whenever a high urinary calcium excretion has been found.

Value of Serum Phosphorus in Diagnosis

The normal serum phosphorus level in adults is 3.2 mg. per cent, plus or minus 0.5 mg.; it is 1 to 2 mg. higher in growing children. Levels below 2.5 mg. occur occasionally in normal persons, but when the level is constantly below 2.5 mg. it is abnormal. There are a few diseases in addition to hyperparathyroidism which are accompanied by a low serum phosphorus concentration. In the vitamin D deficiency diseases, osteomalacia and rickets, as well as in the acquired osteomalacias seen in sprue or in renal tubular defects (Fanconi's syndrome and Milkman's syndrome), the serum phosphorus values usually are low, but in these diseases, for the most part, blood calcium values are normal or low. Furthermore, the clinical picture in these "low serum phosphorus diseases" is not likely to simulate hyperparathyroidism in any other respect.

The combination of a low serum phosphorus and an elevated serum calcium is highly indicative of hyperparathyroidism. This combination is seldom encountered in other diseases, although in rare instances it

may occur in metastatic carcinoma or multiple myeloma.

Factors Obscuring the Low Serum Phosphorus

In several situations the anticipated low serum phosphorus levels of hyperparathyroidism may appear at first glance to be absent. In children with hyperparathyroidism a 1 to 2 mg. allowance must be made for their normally higher serum phosphorus values; thus, normal adult levels may occur in the hyperparathyroid child. Also, in long-standing hyperparathyroidism when hypercalciuria has led to nephrocalcinosis, the phosphate retention which results from the renal insufficiency may partially or completely obscure the expected low serum phosphorus concentration. The following case report illustrates this point satisfactorily.

*Case 2**—A 64 year old woman with diabetes mellitus of eight years' duration presented a typical duodenal ulcer syndrome of four months' duration. Persistent daily vomiting failed to respond to intensive ulcer management, and the x-ray evidence of ulcer crater remained unchanged. Pronounced muscular weakness and absence of all deep tendon reflexes were noted. She had been confined to bed for one year. Reduced renal function was disclosed by urea clearance values of 36 per cent and blood urea concentrations ranging from 56 to 72 mg. per cent. The reduced kidney function was attributed to chronic pyelonephritis and possibly to the Kimmelsteil-Wilson syndrome. An Addis test disclosed 8.6 gm. total protein in a 24 hour urine collection with 56,000 casts. Numerous measurements of serum calcium and serum phosphorus were made. The highest blood calcium measurement was 11.5 mg. per cent but the majority were less than 11.0. The total serum protein content was 6.0 gm. per hundred cubic centimeters. Serum phosphorus values were generally above 3.0 mg., the highest being 4.3; on one occasion it was 1.3 mg. per cent. The alkaline phosphatase measured 3.4 Bodansky units. The Sulkowitch test was intermittently positive. A parathyroid adenoma 2 by 1.2 by .08 cm. in diameter, weighing 0.5 gm., was removed from the lower pole of the left lobe of the thyroid. The ulcer symptoms disappeared, vomiting ceased immediately and in one month the ulcer crater was healed. Subsequent blood calcium levels averaged 9.5 mg. per cent and serum phosphorus averaged 4.6 mg. per cent. Muscular weakness disappeared and deep tendon reflexes returned. The patient has made a full recovery.

This case illustrates the effects of impaired renal function on the level of blood phosphorus in the presence of a parathyroid tumor. It further calls attention to the gastrointestinal manifestations occurring in some patients with the disease. No bone disease was present and there were no kidney stones.

Interpretation of Blood Calcium Values

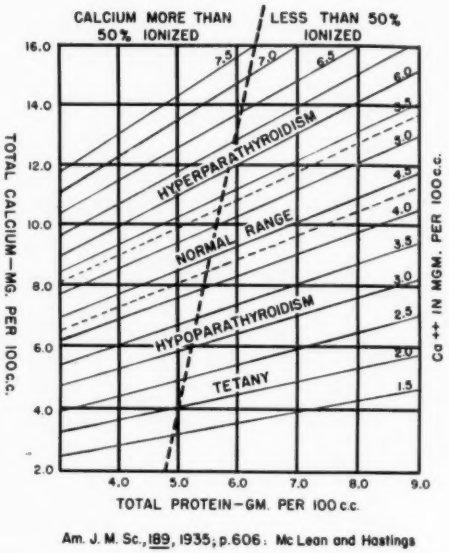
The normal value for blood calcium is 10.0 mg. per cent plus or minus 1.0 mg. This figure represents the total concentration of calcium in the blood and is the sum of two nearly equal fractions. These fractions consist of calcium bound to protein and called calcium proteinate, and unbound or ionizable calcium. The amount of each varies independently, the bound fraction depending on the amount of protein in the blood and the diffusible fraction depending chiefly on parathyroid function. Thus the total calcium measured by laboratory tests will be affected by alterations in either or both of these fractions. For example, a high total serum protein may result in a high total serum calcium in the presence of a normal diffusible calcium and normal parathyroid function. Similarly, hypoproteinemia in the patient with hyperparathyroidism will decrease the total calcium and obscure the degree of hypercalcemia which would otherwise be found. A normal blood calcium in the presence of hypoproteinemia thus becomes an abnormal finding. Suitable corrections in ionizable calcium concentration at varying levels of total blood protein can be obtained from the nomogram of McLean and Hastings (Figure 4). The measurement of the

*For more details concerning this case see the Cleveland Clin. Quart. 18:67, 1951.

total blood protein becomes important in those instances where hyperparathyroidism is under serious consideration but the total blood calcium is not elevated. The anorexia of hyperparathyroidism at times is sufficient to lead to weight loss, undernutrition and hypoproteinemia. The following case report was chosen to illustrate these points.

*Case 3**—A 32 year old man had recurrent right and left renal calculi of one year's duration. The initial stone was composed of calcium phosphate. Progressive fatigue was the only other symptom noted by the patient up to that time. Earlier studies had disclosed serum calcium levels of 12.0, 13.0, 10.7, 12.0 and 11.6 mg. per cent. Serum phosphorus values were 2.2, 1.5, 2.4, 2.2 and 2.4 mg. per cent. Total blood proteins measured 6.9 gm., and 24 hour calcium excretion on a low calcium diet (Aub diet) was calculated to be 445 mg. A diagnosis of hyperparathyroidism was made at that time and he was referred to another institution for surgery; disagreement arose, however, and surgery was postponed. He became anoretic and lost weight, and when he was seen by us for the first time, about six months after the above laboratory procedures had been done, the findings were less definite. Serum calcium values of 10.3, 12.4 and 11.1 were found, while serum phosphorus values remained unchanged. The serum proteins measured 5.2 gm. per hundred cubic centimeters at this time. If the serum protein level had been normal the serum calcium values would have been between 12.0 and 14.0 mg. per cent. The Sulkowitch test was 3+, and x-rays of the teeth disclosed resorption of the lamina dura. A parathyroid adenoma 1 cm. in diameter arising from the left inferior parathyroid gland was found lying deep in the tracheoesophageal groove. Postoperative recovery was complete and subsequent laboratory studies demonstrated serum calcium values of 9.1 and 9.0, serum phosphorus values of 2.2 and 2.7 mg. per cent and, after a month, total protein values of 6.8 gm. per cent.

This case illustrates the value of allowing



Am. J. M. Sc., 189, 1935; p.606: Mc Lean and Hastings

FIGURE 4. Determination of calcium ion concentration from total calcium and total protein values. (Reproduced from McLean and Hastings [Am. J. M. Sc., 1935] with permission of the authors and of the publishers, Lea & Febiger.)

for alterations in total protein when interpreting the levels of serum calcium. It also demonstrates one of the aberrant locations of parathyroid tumors.

It is to be emphasized that many other diseases are accompanied by hypercalcemia. Some of these produce bone changes and are associated with hypercalciuria and renal calculi, but seldom are these conditions accompanied by hypophosphatemia. The following case illustrates a rare exception to this general rule.

Case 4—A 61 year old man with a history of diabetes mellitus of three years' duration noted a rather abrupt onset of muscular weakness, polydipsia, polyuria and nocturia. He had lost 40 pounds in the previous six months. His diabetes had remained well controlled during this time. On examination a palpable mass in the left upper quadrant of the abdomen was noted. A Sulkowitch test disclosed hypercalciuria. Blood chemical findings included a blood calcium of 13.2 and 13.8 mg. per cent, serum proteins of 7.4 gm. per cent,

*For greater details concerning this case see the Cleveland Clin. Quart. 19:66, 1951.

blood phosphorus levels of 2.2 and 2.7 mg. per cent and resorption of the lamina dura. Roentgenograms of the chest disclosed multiple circumscribed densities throughout both lung fields representative of pulmonary metastases. A left retrograde pyelogram showed distortion of the calyces. Autopsy examination verified the clinical diagnosis of hypernephroma.

There is not a constant relationship between hypercalcemia and the symptoms which often accompany it, such as polydipsia, polyuria, nausea, vomiting and muscle weakness. Occasionally symptoms are absent when the blood calcium concentration is excessively high. Furthermore, other causes for hypercalcemia may produce similar symptoms. The following case report illustrates this in a striking manner.

Case 5—A 34 year old mechanic complained of nausea and pernicious vomiting accompanied by muscle weakness, a 40 pound loss in weight, and pain in the back. He had first noted these symptoms nine weeks prior to admission. Physical examination was negative. X-rays of the entire gastrointestinal tract which had been made at two other hospitals had disclosed no abnormality. A diagnosis had not been established. Roentgenologic examination of the chest and of the gastrointestinal tract at the Cleveland Clinic did not disclose the cause of the symptoms. Blood studies demonstrated a severe anemia with 9.5 gm. hemoglobin, 21,200 white blood cells, 20 per cent immature cells, unusually rapid sedimentation rate, serum proteins measuring 6.5 gm. per hundred cubic centimeters, and negative Bence Jones proteins in both blood and urine. X-rays of the skeleton showed many areas of bone destruction. Blood calcium measured 13.6, 15.8 and 13.2 mg. per cent, and blood phosphorus 7.2, 6.0 and 5.2 mg. per cent. The alkaline phosphatase measured 6.0 Bodansky units. The Sulkowitch test was negative on several occasions. Impaired renal function was evidenced by a blood urea of 75 mg. per hundred cubic centimeters and a urea clearance excretion of 28 per cent and 22 per cent of normal. A rib biopsy and examination of the resected specimen established a diagnosis of reticulum cell sarcoma.

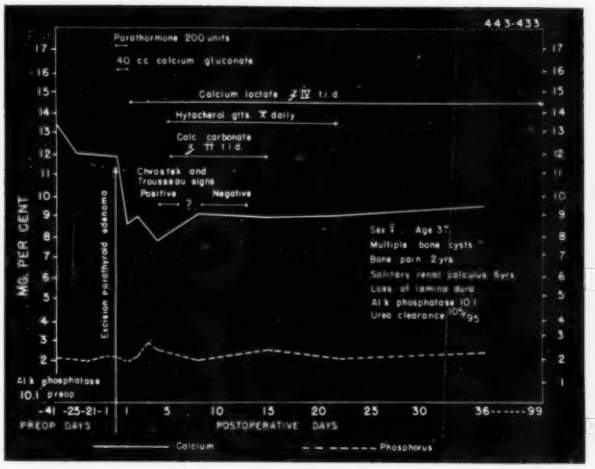


FIGURE 5. Graph showing alterations in blood calcium and phosphorus concentrations after removal of parathyroid tumor. Note length of time tetany persisted, presence of multiple bone cysts and elevated alkaline phosphatase.

This case also illustrates the high phosphorus levels seen in association with impaired renal function. The degree and rapidity of weight loss, the findings of an abnormal hematologic picture, the virtually normal alkaline phosphatase values in the presence of widespread skeletal disease, the absence of hypercalciuria and the rapid sedimentation rate were not in keeping with a diagnosis of hyperparathyroidism.

Value of Alkaline Phosphatase in Diagnosis

The alkaline phosphatase is of extremely limited value in the diagnosis of hyperparathyroidism. It is normal in all cases in which the skeleton is unaffected. It is, in reality, a rather reliable index of the degree of skeletal involvement and, when high, one should anticipate postoperative tetany as calcium flows rapidly back from the blood into the decalcified bones (see Case 1). In this event, the high phosphatase content persists and with it a low serum phosphorus level until skeletal repair is completed (Figure 5).

A normal level of alkaline phosphatase in

a patient with extensive bone disease virtually excludes hyperparathyroidism but is typical of multiple myeloma. The latter disease is frequently confused with hyperparathyroidism; hypercalcemia, hypercalciuria and renal calculi may be present, but roentgenographically the bone lesions in multiple myeloma are usually more sharply demarcated. Bence Jones proteins are present in the urine in only about one-half of the patients. When plasma cells are found in the peripheral blood or in sternal marrow, the differentiation has been established.

Pathology

Hyperparathyroidism can be caused by an adenoma of one or more parathyroid glands, diffuse hyperplasia of all parathyroid glands or carcinoma of one or more parathyroids. In some cases of secondary hyperparathyroidism, hyperplasia is present secondary to an increased demand for parathyroid hormone; the most important of these is that secondary to chronic renal insufficiency. Brief mention subsequently will be made of the findings in such cases.

In primary hyperparathyroidism one is usually dealing with an adenoma of one parathyroid gland. Of 322 cases collected by Norris (Table 2), multiple parathyroid adenomas occurred in 20 (6 per cent). Castleman and Mallory[11,12] reported multiple adenomas in 10 of 160 cases (6 per cent). The great majority of adenomas are located in the lower parathyroids, only 16 per cent of all arising in the upper two. Aberrant parathyroid tumors occur in roughly 10 per cent of all cases (Table 2). Among these the mediastinum is the most frequent site (63 per cent), the remainder being behind the esophagus or trachea, or within the thyroid gland.

TABLE 2

ANATOMIC LOCATION OF PARATHYROID ADENOMAS IN 322 CASES (ACCORDING TO NORRIS[15])

	Per Cent
NORMAL LOCATION	
Right lower	42.7
Left lower	41.1
Left upper	9.1
Right upper	7.1
ABERRANT LOCATION (10.7 Per Cent)	
Mediastinal	63.3
In thyroid	30.0
Behind esophagus	6.7
Multiple adenomas	6.2

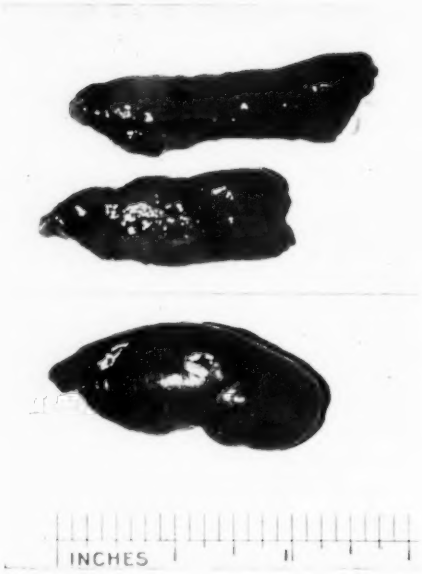


FIGURE 6. Gross appearance of two typical parathyroid adenomas.

Parathyroid tumors are usually soft in consistency, often contain cystlike spaces, are darker brown in color than normal glands (Figure 6) and vary in size from 0.4 gm. to 120 gm. They usually contain chief cells or water-clear cells, but occasionally they may contain only oxyphil cells (Figure 7). In some cases all three cell types are proliferating.

Albright, et al.[13] have emphasized the unusual occurrence of hyperparathyroidism associated with primary hypertrophy and hyperplasia of all four parathyroid glands. This type of pathologic picture is most unusual; the cells are composed of water-clear cells only, each individual cell is two to four times the normal size and the intercellular substance is remarkably scanty. The term hypertrophy is desirable because the microscopic appearance is

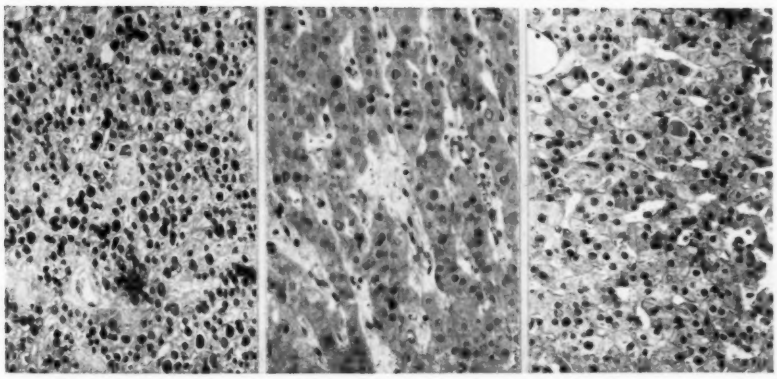


FIGURE 7*a*. Chief cell adenoma. *b*. Dark oxyphil cell adenoma. *c*. Mixed chief cell and oxyphil cell adenoma.

completely different from the hyperplasias of the parathyroid glands secondary to renal insufficiency. (See heading, Secondary Hyperparathyroidism.)

Malignant tumors of the parathyroids are extremely rare. Most of these are not associated with hyperfunction, although occasional cases are, and the symptoms and signs of hyperparathyroidism recur with the return of the tumor. Stephenson[14] reviewed the literature and found 19 examples but, among these, hyperfunction was noted only in 9. The remaining 10 cases are not accepted generally as examples of carcinoma. There has as yet been no uniform agreement among authorities as to what constitutes malignancy of the parathyroids. In those 19 instances, 15 presented palpable tumors. We have observed 4 clinically palpable tumors in the neck in our series of 32 cases of hyperparathyroidism. In 2 of these 4, carcinoma was found. This is in sharp contrast to the finding in benign tumors of the parathyroids; Norris[15] found only 10 per cent palpable preoperatively. Thus, a palpable tumor would appear to increase the likelihood of finding carcinoma at the time of surgery.

Secondary Hyperparathyroidism

Secondary hyperparathyroidism implies parathyroid hyperfunction secondary to increased demand for more parathyroid hormone. The condition is believed to exist in a number of diseases; the chief among these, and the only one to be considered here, is long-standing glomerular nephritis. The glands may be normal or greatly increased in size; they are composed predominantly of normal-sized chief cells with a reduction in intercellular fat tissue.[11,12]

When renal failure is sufficiently severe to lead to nitrogen retention, there is usually an associated phosphorus retention. Hyperplasia of the parathyroids presumably occurs in an attempt to overcome the renal barrier to phosphorus excretion. It is evident that surgical removal of part of the parathyroid tissue under such circumstances should be avoided.

Treatment of Primary Hyperparathyroidism

Surgery is the only satisfactory treatment of primary hyperparathyroidism. Knowledge of the anatomic distribution of parathyroid tumors will greatly facilitate their location and successful removal. The finding of such a tumor may be simple or most difficult. The surgeon should be familiar with their gross appearance and with their differentiation from lymph nodes and other soft tissues in this location.

The frequent location of aberrant parathyroid tissue in the mediastinum (Table 2) cannot be overlooked, and the surgeon should be prepared to explore the mediastinum in all such cases should the need arise. Because the

two lower parathyroid glands are the most frequent sites for the development of parathyroid tumors, and since these two glands develop from the same branchial cleft as does the thymus, their frequent mediastinal location can be readily appreciated.

If a single adenoma is found, one should be content to close the neck and await recovery. If recovery does not occur, the other side can be more readily exposed than would be possible if it were explored at the time of the initial operation. If, on frozen section, the parathyroid enlargement proves to be hypertrophy, then all four parathyroids should be located, three should be removed and approximately 200 mg. of the fourth left in place.

When reduced kidney function is present, or when the skeleton is seriously affected and the phosphatase level is high, it is recommended by some that a portion of the tumor be left behind at the first operation and a second stage done later if necessary. This is recommended in an attempt to avoid postoperative renal insufficiency or extreme parathyroid tetany. At times the tetany is severe and persists for many months until skeletal healing is complete.

Summary

The major clinical manifestations of hyperparathyroidism have been presented. The symptoms induced by hypercalcemia in this and other diseases have been illustrated and the three most common forms of the disease (gastrointestinal, skeletal and renal) have been demonstrated. The diagnostic limitations in the laboratory procedures employed in the study of patients with hyperparathyroidism and other medical diseases of bone have been reviewed. Brief reference has been made to the surgical aspects of the disease, and a word of caution has been given against the surgical treatment of secondary hyperparathyroidism. The greater clinical significance of a low serum phosphorus in the diagnosis of hyperparathyroidism has been stressed in order to emphasize that a low serum phosphorus and an elevated serum calcium are more important when they occur together than when either is present alone.

REFERENCES

1. Albright, F. and Ellsworth, R.: Studies on the physiology of parathyroid glands. I. Calcium and phosphorus studies on case of idiopathic hypoparathyroidism. J. Clin. Investigation 7:183, 1929.
2. Albright, F. and Reifenstein, E.: Parathyroid Glands and Metabolic Bone Disease. Baltimore, Williams & Wilkins, 1942.
3. Morelle, J.: Hyperparathyroïdie. J. de chir. et ann. Soc. belge de chir. 31:381, 1932.
4. Beyerinck, C. W.: Case of tumors of parathyroid gland. Nederl. tijdschr. v. geneesk. 76:3389, 1932.
5. Rogers, H. M.: Parathyroid adenoma and hypertrophy of parathyroid glands. J.A.M.A. 130:22, 1946.
6. Rogers, H. M., Keating, F. R., Jr., Morlock, C. G. and Barker, N. W.: Primary hypertrophy and hyperplasia of parathyroid glands associated with duodenal ulcer. Arch. Int. Med. 79:307, 1947.
7. Schneider, R. W. and Robnett, A. H.: Diagnosis of obscure hyperparathyroidism. Cleveland Clin. Quart. 18:66, 1951.
8. Barr, D. P., Bulger, H. A. and Dixon, H. H.: Hyperparathyroidism. J.A.M.A. 92:951, 1929.
9. Barr, D. P. and Bulger, H. A.: Clinical syndrome of hyperparathyroidism. Am. J. M. Sc. 179:449, 1936.
10. Snapper, I.: Medical Clinics on Bone Diseases. Ed. 2. New York, Interscience Publishers, Inc., 1949, p. 51.
11. Castleman, B. and Mallory, T. B.: Pathology of parathyroid gland in hyperparathyroidism; study of 25 cases. Am. J. Path. 11:1, 1935.
12. ——— and ———: Parathyroid hyperplasia in chronic renal insufficiency. Am. J. Path. 13:553, 1937.
13. Albright, F., Bloomberg, E., Castleman, B. and Churchill, E. D.: Hyperparathyroidism due to diffuse hyperplasia of all parathyroid glands rather than adenoma of one. Arch. Int. Med. 54:315, 1934.
14. Stephenson, H. O., Jr.: Malignant tumors of parathyroid glands; review of literature with report of case. Arch. Surg. 60:247, 1950.
15. Norris, E. H.: Collective review; parathyroid adenoma; study of 322 cases. Internat. Abstr. Surg. 84:1, 1947.

Because of space limitations in this special Cleveland Clinic issue, the concluding section (Part 3) of the article, "The Ever-Continuing Search for Immunity in Tuberculosis," by J. A. Myers, M.D., will be published in the November issue of *Postgraduate Medicine*.

Carcinoma in Rectal Polyp; Follow-Up Observations on 27 Patients

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Radical surgery has often been carried out when cancer in rectal polyp is found or implied in the pathologist's report. A plea is made for a careful consideration of the histologic characteristics of the lesion before the decision for radical or conservative surgery. From the complete histologic picture, an individualized plan of therapy can be established; experience has shown that the majority of these lesions can be treated conservatively.

EVERY physician who has been conscientious enough to perform a biopsy in a case of rectal polyp has occasionally been disturbed by the pathologist's report. The treatment of a benign adenoma of the rectum presents no particular problem, but when cancer in a polyp is found or implied by a diagnosis of "atypism," severe dysplasia, "adenoma malignum" or adenocarcinoma grade 1 in adenoma, special consideration should be given before radical surgery is proposed.

The therapeutic problem comes about because of differences in interpretation and significance of the histologic picture. That differences do occur is reflected by the variations in the reported incidence of carcinoma in polyp. Ten per cent of our biopsied rectal adenomas were malignant, while Klemperer[1] reported an incidence of 14.7 per cent. Swinton's[2] series revealed malignancy in 14 per cent of 827 cases reported. Significant differences in interpretation of the histologic picture and nomenclature are disclosed in a report by Cooper and associates[3] from the Mayo Clinic in which they demonstrated histologically proved adenocarcinoma grade 1 in polyp in 67 of a total of 82 patients thought to have simple adenomas. This represents a high percentage (81.7), undoubtedly due to a less rigid cytologic interpretation for the diagnosis of carcinoma in polyp. Are we to advise radical extirpation of the rectum for this type of carcinoma? Should the diagnosis of carcinoma in polyp be reserved only for invasive carcinoma? Admittedly, exact differentiation between severe dysplasia and noninvasive carcinoma is sometimes difficult, but this type of carcinoma can generally be classified as accurately as that of the skin or cervix and dealt with appropriately.

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Since proctosigmoidoscopy is now more widely practiced, rectal lesions are discovered with greater frequency and office biopsy is an everyday occurrence. The pathologist is often

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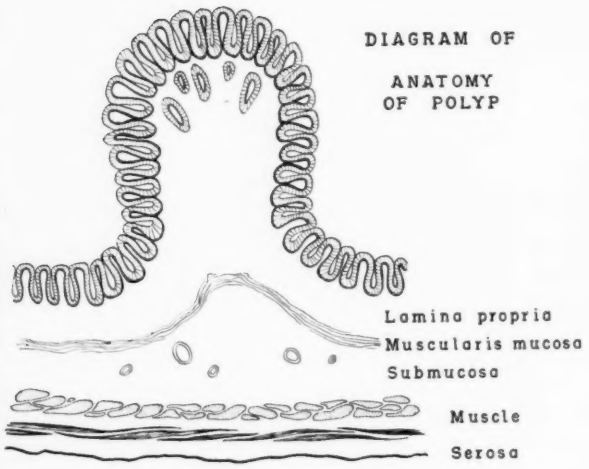

FIGURE 1.

expected to differentiate between benignancy and malignancy in rectal polyps by means of an inadequate piece of tissue removed from the periphery of the lesion. Obviously a complete and final opinion is not always possible under these circumstances and a decision as to the best course of treatment cannot be made. It follows that there must be close cooperation between the surgeon and the pathologist. Sufficient, well oriented tissue must be submitted and a coordinated clinicopathologic interpretation made to avoid inadequate or needless radical surgery.

It has been our belief over the years that the so-called malignant polyp of the rectum could be successfully treated (under certain conditions) by local removal with careful follow-up observation. The purpose of this study is to present the end results of this type of therapy, together with a critical histologic classification. An attempt is made to establish an individualized plan of therapy based on the histologic picture.

Source of Material

Three hundred and fifty rectal polyps were subjected to biopsy during the 10 year period 1939 to 1949 at the Cleveland Clinic and 35 of these were classified as adenocarcinoma[4] arising in polyp (10 per cent). In each instance it was the opinion of the surgeon that the polyp was amenable to local removal or destruction. The entire lesion or adequate portions thereof were submitted for histologic evaluation at the time of treatment. Small or polypoid carcinomas and polyps of familial polyposis were not included, nor were obvious cancers marginated by polyp. Only those tumors accessible to the sigmoidoscope and conforming to the above criteria were selected, since this group may be subjected to unnecessary radical surgery because of a controversial or misinterpreted histologic diagnosis.

Since our previous report,[5] 27 of 35 patients have been followed for 2 to 10 years, leaving 8 unaccounted for.

Pathologic Considerations

Before discussing the end results of conservative treatment of carcinoma arising in polyp, it is important to consider briefly a few fundamental histologic characteristics of these lesions. Frequently, the decision for radical or conservative surgery depends on such an understanding. All glandular polyps, whether having a papillary or a smooth surface, have a similar anatomic structure. The outer surface is composed of glandular elements resembling normal colonic mucosa, although on occasion one observes frequent convolutions, giving the surface a papillary configuration. Separating the glandular elements is a varying quantity of connective tissue stroma, the lamina propria. Beneath this lies the muscularis mucosae (Figure 1). The arrangement of the latter depends on whether the polyp is pedunculated or sessile. In the pedunculated form it is arranged parallel to the long axis of the polyp. The muscularis mucosae separates the superficial portion of the polyp (mucosa) from the underlying submucosa of the segment from which the polyp has arisen. It is important to realize that the so-called "stalk" of the polyp is formed by this submucosa with its attendant lymphatic and vascular channels. It becomes apparent that a carcinoma arising in a superficial portion of a polyp (mucosal portion) might be adequately treated by local means, whereas

TABLE 1

CARCINOMA ARISING IN RECTAL POLYP

TYPE OF CARCINOMA	PATHOLOGIC CHARACTERISTICS
Noninvasive	
Carcinoma *in situ*	Cytologic carcinoma without invasion of basement membrane
Superficial adenocarcinoma	Carcinoma with reduplication of lamina and invasion of basement membrane and lamina propria
Invasive	Carcinoma with invasion of muscularis mucosae and presence of desmoplastic tumor stroma

one which has invaded the muscularis mucosae and underlying submucosa gains access to the lymph and vascular channels and would require more radical therapy to insure cancer control.

Carcinoma in polyp has been divided into invasive and noninvasive types, with special reference to the muscularis mucosae (Table 1). Noninvasive carcinoma includes carcinoma *in situ* and superficial carcinoma. Carcinoma *in situ* is characterized by anaplasia and irregularity of the glandular epithelial elements without evidence of invasion of the surrounding lamina propria (Figure 2a and b). Superficial carcinoma, in addition to the anaplasia and irregularity of carcinoma *in situ*, demonstrates invasion of the lamina propria by nests of tumor cells (Figure 3) as well as marked reduplication of neoplastic lumens. No evidence of muscularis mucosal invasion is demonstrable in superficial carcinoma.

Invasive carcinoma demonstrates invasion of the muscularis mucosae (Figure 4a) or actual penetration of lymphatic or vascular structures. This type of carcinoma further demonstrates a desmoplastic tumor stroma (Figure 4b) which is not observed in the carcinomas of the noninvasive group.[6]

Such a descriptive classification provides a better understanding of the type of carcinoma encountered in polyp. Because of the therapeutic implications of a diagnosis of "cancer in polyp," such an exacting histologic examination of these lesions is indicated. For ideal evaluation of the lesion there must be

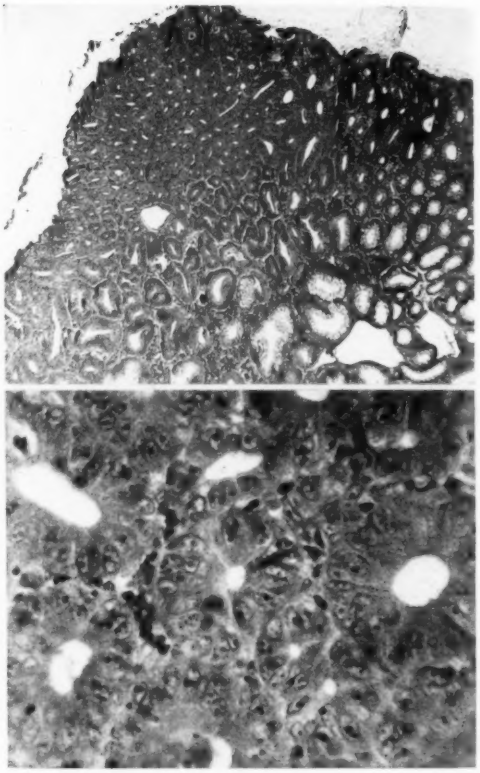

FIGURE 2*a*. Low power focus of carcinoma *in situ* arising at edge of polyp (x 50). *b*. High power focus from same area as in *a*. Note atypical cells—macronucleoli.

FIGURE 3. Superficial carcinoma arising in polyp at upper left. Note glandular budding. No evidence of desmoplastic tumor stroma (x 70).

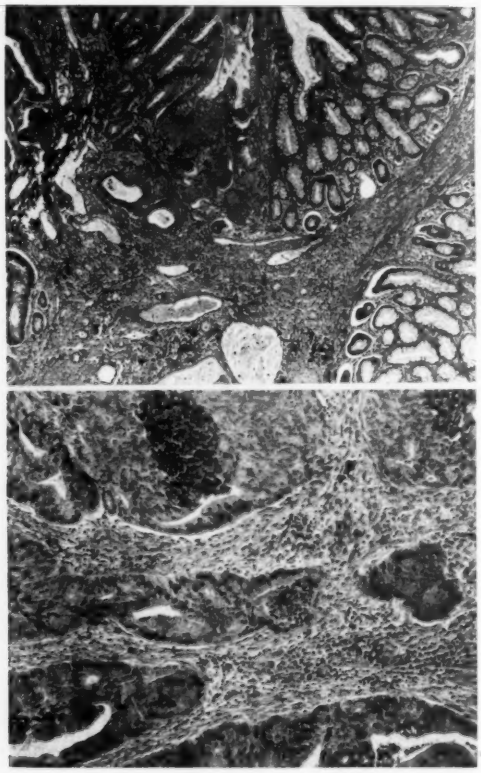

FIGURE 4*a*. Carcinoma invading muscularis mucosae at left (x 70). *b*. Another area from the same tumor as in *a* with desmoplastic tumor stroma (x 70).

close cooperation between the surgeon and pathologist, and the former must supply adequate tissue for examination. If at all possible, complete excision biopsy is most desirable so that many areas of a given polyp may be examined. If this is not feasible, as in certain diffuse, high-lying lesions, multiple biopsy from many areas will often be satisfactory.

Treatment

The most desirable treatment of rectal polyp is surgical excision. In this manner the entire tumor can be submitted for pathologic study and there is a minimum of scarring. In general, tumors located within 3 to 4 inches of the anal verge may be delivered into the lower rectum or to the outside, depending on their mobility. Unfortunately those located higher are less accessible and it is necessary to biopsy the polyp from all areas to have a fair histologic evaluation.

Fulguration is the safest method of destruction of polyps. Care must be taken above the peritoneal reflection so that perforation does not occur, and caution must be exercised when the lesion is located over the bladder neck or vagina, as damage to these structures may result. Certain small polyps 1½ cm. in diameter may be treated as an office procedure providing the base or pedicle is visualized and biopsy is adequate. Patients with larger lesions should be hospitalized, and the operating proctoscope and pudendal block anesthesia utilized. Since mucosal surfaces are painless, anesthesia is necessary only to introduce the operating proctoscope through the rectal sphincters. Spinal or caudal injection may add morbidity to the procedure. Fulguration, utilizing a ball tip electrode, destroys the adenomatous surface by charring, and it is better to apply this method at monthly intervals than to attempt total ablation at one time. There will be less scarring and damage to underlying structures, particularly where wide-based adenomas are treated. Radon seed implantation as used in this series is of value mostly to prevent late hemorrhage at the time of slough of the charred stump. Stricture may occur at the rectosigmoid junction and particularly when the treated tumor lies on one of the valves of Houston. If patients are seen at monthly intervals, strictures can easily be dealt with by bouginage with excellent and permanent results.

Results of Treatment

Twenty-seven patients having carcinoma in rectal polyp have been followed for 2 to 10 years (Figure 5). All patients were treated by local excision, coagulation or radon seed implantation, or by combinations with the latter. Sixteen lesions proved to be noninvasive carcinoma and 11 were invasive. The invasive group did not have radical surgery because of advanced age or infirmity. The incidence of carcinoma arising in polyp was found to be most frequent in the fifth and sixth decades of life, with the average age

being 60.2 years. It is significant that no person in this series has died of recurrence or metastasis from the original tumor and that the deaths have been due to another primary lesion located above the rectum, other malignancies, or to unrelated conditions. Of the 27 reported cases, 2 have succumbed to undetected primary carcinomas of the colon above, while 2 others have recently returned for the removal of carcinomas located in, the sigmoid colon.

Although complete destruction of some large polyps at monthly intervals took as many as four or five treatments, it is significant that there was no local recurrence in any patient after one year.

Discussion

The reported results of local treatment in noninvasive carcinoma in polyp in this series are of value only when combined with the reports of others. Twelve of the 16 have been followed for 5 to 10 years without evidence of recurrence. McLanahan, et al.[7] (25 cases), Swinton[4] (22 cases) and Castro, et al.[8] (9 cases) have reported follow-up studies of from five to seven years of comparable lesions without fatality, thus making a total of 68 such lesions treated locally without recurrence.

It is believed that noninvasive carcinoma can be treated by local obliteration rather than radical surgery, providing the tissue for biopsy is representative of the lesion. Patients with diffuse lesions with or without noninvasive malignant change must be treated by more radical means in order to obliterate the lesion. Pull-through operations with preservation of the sphincters are safe in these cases.

The 7 surviving patients with invasive cancer in polyp who are living and well from four to five years after treatment may not be representative of a larger group. It must not be construed from this result that this is the procedure of choice, since it is our belief that invasive cancer in polyp should be treated by radical surgery. It is worth while to know, however, that certain justifiable liberties may be taken with aged and bad-risk patients.

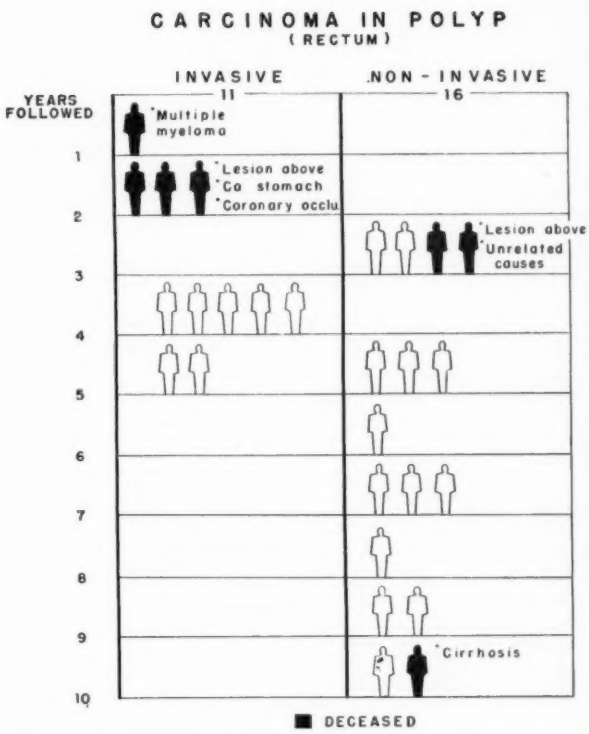

FIGURE 5. Follow-up observations on 27 patients treated by coagulation and radon seed implantation.

REFERENCES

1. Klemperer, P.: Studies of adenomatous polypi and carcinoma of colon. Am. J. Digest. Dis. 5:566 (November) 1938.
2. Swinton, H. W. and Warren, S.: Polyps of colon and rectum and their malignancy. J.A.M.A. 113:1927 (November 25) 1939.
3. Cooper, W. L., Buie, L. A. and McDonald, J. R.: Adenoma of rectum and lower portion of sigmoid. Am. J. Surg. 82:546 (November) 1951.
4. Swinton, H. W.: Diagnosis and treatment of mucosal polyps of rectum and colon with early malignant change. Am. J. Surg. 75:369 (February) 1948.
5. Fisher, E. R. and Turnbull, R. B., Jr.: Malignant polyps of rectum and sigmoid; therapy based upon pathologic considerations. Surg., Gynec. & Obst. (In press.)
6. ——— and ———: The differentiation of noninvasive and invasive carcinoma arising in intestinal polyp. Cleveland Clin. Quart. 19 (No. 2), April 1952.
7. McLanahan, S., Grove, G. P. and Kiefer, R. F.: Conservative management for certain rectal adenomas showing malignant change. J.A.M.A. 141:822 (November 19) 1944.
8. Castro, A. F., Ault, G. W. and Smith, R. S.: Adenomatous polyps of colon and rectum. Surg., Gynec. & Obst. 92:164 (January) 1951.

The Treatment of Duodenal Ulcer

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The importance of the treatment of duodenal ulcer is apparent from the fact that 10 per cent of adult males have or have had an ulcer. Treatment consisting of an hourly ulcer schedule, with food or milk on the even hours and antacids on the odd hours, is outlined. Encouraging results have been obtained with a new anticholinergic drug (BANTHINE®). *The use of banthine or other new anticholinergic drugs as an adjunct to the routine ulcer treatment outlined is recommended. When surgery is necessary for duodenal ulcer (as in 10 to 15 per cent of our patients), we believe vagotomy with gastroenterostomy is usually the operation of choice.*

C. H. BROWN

At the Cleveland Clinic we are seeing an increasing number of patients with duodenal ulcer. A study of available figures indicates that 10 per cent of adult males have or have had a duodenal ulcer.[1] The economic importance of duodenal ulcer cannot be overemphasized when one considers the days lost from work and the lowered efficiency resulting from ulcer distress. With the high incidence of duodenal ulcer, its treatment becomes more and more important. In this paper we shall present a modified Sippy type of program, results with a new anticholinergic drug (banthine), current treatment of some of the complications of duodenal ulcer and, finally, surgical results with vagotomy and gastroenterostomy.

Peptic ulcer is any ulceration in the gastrointestinal tract caused by the peptic activity of the gastric juice. Sites that may be involved are (1) the esophagus from regurgitation of acid gastric juice or associated with heterotopic gastric mucosa, (2) the stomach, (3) the duodenum, (4) Meckel's diverticulum, also associated with heterotopic gastric mucosa, and (5) the site of a gastrojejunostomy—a marginal ulcer.

Certain physiologic facts are important in any discussion of peptic ulcer. Peptic ulcer is dependent on the formation of acid gastric juice. It does not occur in the absence of free hydrochloric acid, and when the acid is neutralized the ulcer heals. The *p*H of the gastric juice in patients with a duodenal ulcer is between 1 and 4. Above a *p*H of 4, peptic activity is eliminated. The objective in treating an ulcer is to decrease the acidity and consequently the peptic activity of the gastric juice. If the *p*H is kept above 4, peptic activity is eliminated and the ulcer heals.

Duodenal ulcer differs from gastric ulcer in several respects:

1. In gastric ulcer there is normal or subnormal gastric acidity, although never complete anacidity to histamine.[2]

2. In duodenal ulcer there is increased gastric acidity, continual night secretion and higher volume of gastric secretion. The continual night secretion does not occur in normal persons or in patients with gastric ulcer.[3-5]

3. In duodenal ulcer, Vanzant has shown an increase in the secretion of pepsin.[6]

4. Duodenal ulcer is a disease of civilization. There is a higher incidence in extensively industrialized countries such as our own whose people are subjected to nervous tension, and increased incidence in the city over the rural dweller and in the Northern Negro over the Southern Negro. This is not true of gastric ulcer.

5. The patient with duodenal ulcer fits a definite personality pattern[7] not usually present in gastric ulcer patients. The duodenal ulcer patient is outwardly calm but inwardly tense; overambitious with excessive drive; a hypersensitive individual; a chronic worrier over small things, and an uneasy soul who becomes discontented with idleness. He is frequently restless. Few of these persons are fishermen—they simply do not have the patience. There is a preponderance of the vagus influence, and many ulcer patients will show other signs of vagotonia such as hypotension, bradycardia and signs of hypothyroidism.

6. Carcinoma is not associated with duodenal ulcer. Gastric ulcers may be malignant, and many believe that they may undergo malignant transformation.

Gastric ulcer and duodenal ulcer are two separate diseases. The etiology of gastric ulcer is obscure, but we feel that a great deal is known concerning the etiology of duodenal ulcer. The increased nervous tension of the patient's personality pattern precipitates increased vagal discharges, increased gastric secretion and spasm and, eventually, ulcer. There is also an antiulcer factor which prevents digestion by the normal stomach. Whether this is due to the mucin present or to other factors is not known.

Any treatment of duodenal ulcer must modify or break the preceding chain reaction in order to be effective. Psychoanalysis attempts to modify the personality but is difficult and time-consuming and its effectiveness is questionable. Psychoanalysis is an impractical treatment for a disease as common as duodenal ulcer. Vagotomy and vagal-blocking drugs are effective in interrupting the cycle by preventing the nervous impulses from causing the excess acid secretion. The Sippy type of program of neutralizing gastric acidity abolishes the effects of the excessive vagal stimulation. Gastric resection acts by removing the acid-secreting cells, and the value or success of the resection is dependent strictly on the amount of stomach resected and the degree to which the gastric secretions are changed.

Routine Ulcer Management

A modified Sippy program is used at the Cleveland Clinic in treating active duodenal ulcers:

1. One of the most important factors is the treatment of nervous tension, and anything that contributes to its relief is especially helpful. If the patient is employed on an irregular schedule, such as night shifts or split shifts, an effort should be made to transfer his activity to day work. The physician's efforts in adjusting the patient's emotional life both at work and at home are important.

2. The patient is asked to avoid those things that increase gastric acidity. Coffee, tea and cola beverages are stimulants to gastric acidity and should be avoided, as should all forms of alcohol. The use of tobacco is discouraged.

3. A fairly liberal bland diet is prescribed. allowing meat, cooked fruit and cooked vegetables. The patient is instructed to eat or to drink a glass of milk every two hours on the even hours.

4. An antacid (an aluminum hydroxide preparation with magnesium trisilicate[8]) is ordered, two teaspoons every two hours on the odd hours. Calcium carbonate and other antacid preparations may be just as efficacious. On this regimen the patient has something in his stomach to neutralize acidity every hour, with food or milk on the even hours and antacids on the odd hours. It is not sufficient to tell the patient to take alkalis

when he has distress or three or four times a day; in order that the ulcer may heal an hourly schedule is necessary.

5. Sedation with phenobarbital, antispasmodics such as tincture of belladonna, and vitamin supplements are used as indicated.

The treatment outlined is continued for two months. A progress x-ray of the stomach is then obtained, and if the ulcer has healed a modified ulcer program is followed. This less rigorous regimen is used to prevent recurrences of the ulcer and is continued indefinitely:

1. Continued avoidance of nervous tension and of coffee, tea, cola drinks and alcohol.

2. Bland diet with milk two hours after each meal.

3. Antacids one hour after each meal and at bedtime.

There are certain circumstances in which a patient with a history of duodenal ulcer may anticipate a flare-up of his ulcer. The hourly schedule of treatment is resumed under any of these circumstances:

1. Circumstances which increase nervous tension—emotional stress such as may be aggravated by business or domestic difficulties.

2. Any intercurrent infection such as influenza and acute upper respiratory infections.

3. Any surgical procedure, even a simple one like herniorrhaphy or prostatectomy.

4. In the spring and fall in the event the patient has experienced previous recurrences; this should be anticipated and avoided by several weeks of intensive ulcer treatment.

5. Immediately, with any recurrence of ulcer symptoms.

Because of the basic nature of the disease, the pressure under which we live and the intrinsic personality of the ulcer patient, it is characteristic that recurrences are frequent. By following a modified ulcer program, such recurrences may be prevented.

Results of Treatment with Banthine

A small group of patients continue to have ulcer recurrences despite advice, often because they will not or cannot follow the suggested ulcer program. Because of this small group of "intractable" patients and because of the difficulty many patients have in following an hourly schedule while continuing to work, there is always interest in any new drug that may prove effective in the treatment of duodenal ulcer.

Longino, et al.[9] reported that banthine caused prolonged depression of gastrointestinal motility and usually a reduction in volume and acidity of secretion from the stomach. Grimson[10] discussed the beneficial use of banthine in 100 patients with duodenal ulcer. Dragstedt and his group[11] found that this drug produced a "marked reduction in the secretion of gastric juice in dogs, and a marked reduction in the nocturnal gastric secretion of peptic ulcer patients."

Banthine has an anticholinergic action and also provides an autonomic ganglion block. Vagal-blocking drugs (and vagotomy) are effective in the treatment of duodenal ulcer by decreasing acid secretions and by suppressing the vagal stimulation—in other words, by preventing the excess secretion of acid.

From January 1950 to January 1951 banthine was administered at the Cleveland Clinic[12,13] to 117 patients with duodenal ulcer and to 20 patients with other gastrointestinal disturbances. All patients were followed for a minimum of two months. They were given 100 mg. (2 tablets) of banthine every six hours around the clock. In order to evaluate the drug, most of the patients used only a general simple diet without antacids or other medications. They were denied coffee, tea and alcohol. Most of these patients had experienced symptoms for a considerable period of time, the average being 5.9 years. The majority had had repeated recurrences despite previous ulcer treatment, and many had been advised to undergo surgery. Twenty-one patients gave a history of hemorrhage, 7 of obstruction and 9 of a previous perforation. Many of these patients can be classified as having an intractable ulcer, as demonstrated by the preceding complications.

The symptomatic response of these patients to banthine is presented in Table 1. Ninety-seven of 117 patients experienced prompt relief. Comments of many of these patients—"Best medicine I ever had," "Feel better than

TABLE 1

SYMPTOMATIC RESPONSE TO BANTHINE

	NUMBER OF PATIENTS
Prompt relief of distress	97
Definite relief with occasional distress	2
Partial relief	5
Asymptomatic when given banthine, but persistent crater as shown on x-ray	6
Intolerance to banthine	2
Favorable response, then recurrence	1
Increased symptoms	2
No relief	2
TOTAL	117

TABLE 2

ROENTGENOLOGIC RESPONSE TO BANTHINE THERAPY

	NUMBER OF PATIENTS
Ulcer crater disappeared	55
Ulcer crater reduced	5
No change in crater	3
Crater recurred	2
Indeterminate (deformity ?, crater ?, accessory pocket)	4
TOTAL	69

I have in 10 years," etc.—were most gratifying. Relief from distress usually occurred within two to three days. Two patients had occasional distress, and 5 patients obtained only partial relief. Six patients had no symptoms when they were given the drug, their symptoms having subsided on the ulcer program previously outlined; they were given banthine because of persistence of the ulcer crater on x-ray examination. Two patients did not tolerate the medication. The results in 1 case suggested that the patient may have developed a tolerance to the medication, as he responded initially but later developed a recurrence while still taking the medicine. Two of the failures were due to duodenal obstruction; banthine resulted in an increase in distress and vomiting caused by a decrease in gastric motility. *Banthine should not be prescribed for a patient with obstruction until the obstruction has been relieved* by the usual medical means which will be described later. Five other patients with obstruction responded to banthine after the obstruction had been relieved. Five patients with recent massive gastrointestinal hemorrhage were treated in the usual manner before banthine was administered.

Progress x-ray examinations of the stomach were obtained in 69 patients; the results are presented in Table 2. In some of the cases an ulcer crater was not demonstrated on the original roentgenologic examination; hence progress studies in these patients were without value.

From a roentgenologic viewpoint, an excellent response to banthine was obtained in 60 of 69 patients, a most satisfactory result, with only 5 failures. There was no change in the size of the crater in 3 patients. In 2 patients there was a disappearance of the crater on initial banthine therapy; later, while still on the medication, there was a recurrence of the crater. This again suggests the possibility that patients develop tolerance to the medication.

There were no toxic or severe reactions from the medication although it was necessary to discontinue the drug in 8 patients (5 per cent) and to decrease the dose in 22 others (15 per cent) because of side reactions. These consisted of dryness of the mouth, some urinary retention and frequency, slowing of the urinary stream and impairment of visual accommodation. Thirty-seven other patients experienced similar reactions but were not too uncomfortable and were able to maintain the full dosage of the medication.

The symptomatic and roentgenologic response of our patients to banthine suggests that it may have an extremely useful function in the treatment of duodenal ulcer. The side reactions are somewhat troublesome and limit its use. One notes that 20 per cent of the patients did not tolerate the full dose. For this reason we have thought it best, at the present time, to reduce the dose of banthine to 1 tablet (50 mg.) with each meal and 2 tablets (100 mg.) at bedtime, and to combine its use with the modified ulcer program already outlined.

There are contraindications to the use of banthine that should always be remembered: (1) The drug should not be given to anyone with an incipient glaucoma, as the medication may increase the intraocular pressure; (2) in

cardiac conditions, such as coronary insufficiency and cardiac decompensation, the use is contraindicated since banthine increases the heart rate; (3) in bladder neck obstruction it is also contraindicated, because the drug decreases the motility of the urinary bladder; 1 patient who was given banthine by his local druggist without a prescription developed acute urinary retention; (4) in achalasia or cardiospasm, banthine is contraindicated since it is possible to produce this condition in dogs by performing a high vagotomy, and (5) it is temporarily contraindicated in pyloric obstruction until the obstruction has been relieved by other medical means.

There have been a number of reports on other drugs which are said to act in a manner similar to banthine. British investigators[14] have reported that hexamethonium chloride and bromide are effective in reducing gastric secretion. These drugs are disadvantageous in that they produce hypotension and must be given parenterally to be effective. We have had experience with PRANTAL®* in 30 patients. The dosage recommended—50 mg. four times a day—has usually been inadequate in controlling symptoms. A greater dose—100 or even 200 mg.—must be given every six hours. Prantal has fewer side reactions than banthine but does not appear to be as effective. The Upjohn Company has two new preparations, as yet unnamed, with which we have had no experience. Kirsner, et al.[15] reported that these new products are fairly effective in the reduction of free acid and of the volume of gastric secretion when given intramuscularly. A completely satisfactory anticholinergic, antisecretory drug for the treatment of duodenal ulcer has probably not been made as yet, but the development of these newer drugs indicates considerable promise.

Some of the newer anticholinergic drugs may be more effective and have fewer side reactions than banthine. The crux of the problem of duodenal ulcer is the prevention of recurrences. Whether smaller doses of some of these newer drugs will prove effective or whether patients will develop tolerance to the drugs is not known. The fundamental basis for the treatment of duodenal ulcer is still the modified Sippy program. The most judicious therapy, and that which will give the best results, is undoubtedly a combination of the Sippy program outlined and one of the potent new anticholinergic drugs such as banthine. The anticholinergic drugs may make it possible to decrease the frequency of antacids and between-meal feedings.

Two other drugs should be mentioned: (1) enterogastrone, which does not reduce the gastric acidity and is of questionable effectiveness; in addition, the cost is prohibitive, and (2) KUTROL®, which does not reduce the acidity. The latter drug was entirely ineffective in our experience four years ago.

Treatment of Complications of Duodenal Ulcer

Posterior penetration of a duodenal ulcer probably occurs more frequently than is commonly recognized. This penetration may cause severe intractable pain not promptly responsive to ulcer treatment, pain radiating into the back and severe night pain. It is necessary for patients with such an ulcer to follow a more intensive type of treatment. A Levin tube with continuous Wangensteen suction or a milk drip[16] to which has been added sodium bicarbonate will frequently relieve the night distress.

Perforation—Most physicians still believe that the best treatment for an acute perforation is simple operative closure as soon as possible. Definitive surgery such as a vagotomy with gastroenterostomy, or a gastric resection, is contraindicated at this time. The usual practice at the Cleveland Clinic has been to operate on patients in whom the perforation may be presumed to have occurred not more than 10 to 12 hours previously. If the perforation has occurred more than 24 hours previously, spontaneous walling-off may be assumed to be taking place, and treatment such as constant gastric suction with antibiotics is often preferable. Although optimistic reports of conservative therapy for all perforations are increasing in the literature, it is obvious that patients treated in this way

*Methylsulfate (Schering Corporation).

demand the closest bedside care and nursing supervision, which may be unavailable.

Obstruction—Inflammation, edema or spasm rather than stenosis from scar tissue is the responsible factor in at least 90 per cent of the patients with obstruction. These patients can be treated medically with Wangensteen suction at night and a restricted diet of fluids and hourly antacids by day. Usually after one week on this regimen, patients can be placed on the routine ulcer program already outlined. It is remarkable how quickly a dilated stomach can return to normal on such treatment. With more than one recurrence of obstruction, surgery is usually advisable.

Hemorrhage—At least 90 per cent of patients with massive hemorrhage from a duodenal ulcer are medical problems and do not require surgery. However, ideal management includes attendance by a surgeon[17,18] in the event an operation must be performed. Bleeding ceases in most cases on an adequate medical program. If there is any question about the diagnosis of a duodenal ulcer, roentgenologic examinations should be made during the first 24 hours. Only gentle palpation is necessary. (If such x-rays are postponed too long, the responsible ulcer may heal and defy roentgenographic diagnosis.)

The bleeding patient should not be given morphine, as this drug may actually increase the bleeding and aggravate the nausea and vomiting. Sedation with sodium phenobarbital (1 or 2 gr.) and atropine sulfate (1/100 gr.) is given hypodermically and repeated every two to four hours. Bland feedings are prescribed every two hours and antacids are given between each feeding. The antacids are repeated during the night.

Blood transfusions are of paramount importance. At least 3 pints of blood should be ready for any emergency. Blood is essential to combat shock and raise the blood pressure. It is best to raise the hemoglobin to 10 gm. and to keep it at this level, since it gives the patient a much greater margin of safety should bleeding recur.

Hourly blood pressure and pulse rates are determined and charted. Daily blood urea, hemoglobin, red blood cell count and stool examinations are done. If the pulse rate continues to rise and the blood pressure to fall in spite of continuous blood transfusions and the use of the procedures outlined, surgical intervention is indicated. If surgery is to be performed for the acute, massively bleeding duodenal ulcer, it should be done generally within the first 48 hours. If bleeding recurs after it has been arrested, and the patient again goes into shock, surgery is indicated.

On the outlined program it rarely becomes necessary to operate on a bleeding ulcer. If surgery is indicated, a gastric resection should be done with exclusion of the ulcer and ligation of the bleeding vessel. We have seen patients continue to bleed after a vagotomy for an active bleeding ulcer; vagotomy is contraindicated when active bleeding is present.

If the patient has experienced two episodes of massive gastrointestinal hemorrhage we believe that elective surgery, after an episode of bleeding, is indicated when the patient is in good condition for operation. Vagotomy with gastroenterostomy is the preferred procedure in such cases.

Carcinoma is not a complication of duodenal ulcer. The development of carcinoma of the stomach in a patient with duodenal ulcer is actually unusual. It is important to reassure the patient in order to allay unfounded fear and anxiety.

Surgical Results

Since some patients either cannot or will not stay on a medical program and since a very few may have ulcers which will not respond, some have repeated recurrences. The question of surgery arises in from 10 to 15 per cent of patients having duodenal ulcer, and in recent years from 10 to 15 per cent of our patients have been subjected to surgery.

Levin, Palmer and others[2-5] have shown that patients with duodenal ulcer have increased nocturnal secretion of acid gastric juice. Dragstedt[19] found that complete vagotomy reduced the gastric secretion in dogs 76 per cent and that the output in duodenal ulcer patients was reduced to an amount below the normal level by complete vagotomy. The

physiologic basis for vagotomy in duodenal ulcer is based on two findings: (1) that duodenal ulcer patients have increased nocturnal secretion of acid and (2) that vagotomy abolishes this increased secretion.

Excellent results in the use of subdiaphragmatic vagotomy have been reported by Dragstedt and his group,[20,21] by Cleveland Clinic investigators,[22-25] by Grimson and many others. Dragstedt, who had done 521 vagotomies prior to 1949, reported 86 per cent excellent results with vagotomy and gastroenterostomy.

Walters[26] and others believe their results with vagotomy are no better than with gastroenterostomy alone. Because there is still considerable confusion concerning the results obtained with this procedure, we reviewed those obtained in the first 154 patients who had had vagotomy with gastroenterostomy at the Cleveland Clinic.[27] Only those undergoing vagotomy with gastroenterostomy were included in this survey; vagotomy with gastric resection or with pyloroplasty, vagotomy alone, etc. were not included.

We were unable to obtain a follow-up on 7 patients, so 147 patients (95 per cent) were followed. These patients were operated on between September 1946 and March 1949. The length of the follow-up is given in Table 3 and is now approximately nine months longer than when this survey was made. We are still following these patients.

TABLE 3

DURATION OF FOLLOW-UP

YEARS	NUMBER OF PATIENTS
2	78
3	53
4	16
TOTAL	147

Table 4 shows the duration of symptoms and indicates that most patients had had symptoms for a considerable time before operation and had experienced repeated recurrences before surgery was advised. Only patients with severe, intractable ulcers or with other complications are advised to undergo surgery at the Cleveland Clinic.

TABLE 4

DURATION OF SYMPTOMS

YEARS	NUMBER OF PATIENTS
1 or less	3
2 to 4	17
5 to 9	36
10 to 14	28
15 to 19	21
20 and over	42
TOTAL	147

The age is important in the patient about to be operated on, because a gastroenterostomy alone in the older age group frequently produces good results. From Table 5 it can be seen that most of the patients were not in this older age group in which satisfactory results from gastroenterostomy alone might be expected. Only 15 were over 60 years of age.

TABLE 5

AGE DISTRIBUTION

AGE (YEARS)	NUMBER OF PATIENTS
20-29	6
30-39	25
40-49	48
50-59	53
60-69	14
Over 70	1
TOTAL	147

The indications for surgery in this group of patients are shown in Table 6. The number totals more than 147 because many patients had two or more such indications, e.g., a patient may have had an intractable ulcer with repeated recurrences despite medical treatment, a history of hemorrhage, and perhaps obstruction. From this table it can be seen that surgery was not lightly advised, that it was not suggested until there had been a thorough trial on medical programs and that most patients had intractable ulcers.

The results obtained are presented in Table 7. One hundred and one patients or 68.7 per cent reported excellent results. These patients followed no diet, took no medication and had neither gastrointestinal distress nor disturbance. The results were good in 31 or 21.1 per cent. These patients did not experience any

TABLE 6

INDICATIONS FOR SURGERY

INDICATION	NUMBER OF PATIENTS
Intractability	75
Obstruction	59
History of hemorrhage	39
Previous perforation	12
Question of neoplasm	2

TABLE 7

RESULTS OF VAGOTOMY WITH GASTROENTEROSTOMY

RESULTS	NUMBER OF PATIENTS	PER CENT
Excellent	101	68.7
Good	31	21.1
Improved	5	3.4
Failures	10	6.8

ulcer distress, but occasionally had transient diarrhea, gas and other gastrointestinal disturbances. None of this group took medication or stayed on any particular diet after surgery.

Five patients were classified as improved. Although they experienced more distress, had to stay on a diet and occasionally took some medication, none had recurrence of ulcer symptoms. Only 10 patients (6.8 per cent) were classified as failures; in these cases there were recurrent ulcer symptoms, with a demonstrable marginal ulcer in 6. Therefore, 90 per cent of our patients had satisfactory results.

The relatively benign course following surgery can be noted by the length of time the patients remained in the hospital after operation. The majority of patients (110) went home on the tenth postoperative day or sooner. Patients with severe ulcer distress and considerable night pain difficult to control medically had immediate relief following vagotomy with gastroenterostomy. The mortality resulting from the operation has, in our experience, been only 0.6 per cent; 358 patients had undergone this procedure through May 1951, with only 2 operative deaths.

These results appear more promising than those obtained by gastric resection at the Cleveland Clinic. It should be noted that we prescribe no diet or medication following operation, allow the patient to eat what he likes and do not prohibit coffee, alcohol or tobacco. This is in direct contrast to the advice given to many patients in other clinics following gastric resection where frequently the patients are instructed to continue the ulcer diet, to take antacids and to follow other aspects of the ulcer program. We do not believe that an operation requiring a postoperative regimen which limits the diet and requires continued medical therapy solves the patient's problem.

There are two principal objections to gastric resection: (1) It is an intrinsically hazardous procedure which, in the hands of master surgeons, still has a mortality rate of 2 to 4 per cent. The mortality in operations performed by the average surgeon can only be conjectured, but it is certainly much higher; (2) many patients who have had two-thirds or more of the stomach removed cannot be considered "normal" from a digestive standpoint. While free from ulcer symptoms and the complications of ulcer, a substantial proportion of postgastrectomy patients fail to regain their normal weight, often suffer in some degree from "stomach consciousness," anemia, malnutrition or the dumping syndrome, or must follow a restricted diet. The surgeon performing a gastric resection for duodenal ulcer still faces a dilemma: The less stomach he removes, the more likelihood there is of recurrent ulceration; the more stomach he removes, the more likely are other sequelae.

Because of our success with vagotomy and gastroenterostomy, we have discontinued doing gastric resection for duodenal ulcer except in an unusual situation, and there are certain circumstances in which we believe a vagotomy is not indicated. Gastric resection is the operation of choice for a "pyloric" ulcer or if there is a coexistent gastric ulcer. Since excess vagal stimulation seems to play no part in the etiology of gastric ulcer, gastric resection rather than vagotomy should be performed as the surgical treatment of gastric ulcer. If there is active bleeding at the time of operation, a gastric resection is indicated. A gastric resection rather than a vagotomy should be done if there is technical dissatisfaction with the vagus resection such as might

occur if there has been a previous peritonitis with adhesions around the hiatus of the diaphragm. In addition, in the presence of an active perforation, simple closure of the perforation should be done; performing definitive surgery at that time, in the presence of infection, entails added risk.

As already stated, our results with vagotomy with gastroenterostomy for duodenal ulcer are excellent. We prefer vagotomy with gastroenterostomy to gastric resection for the following reasons: (1) lower mortality with vagotomy and gastroenterostomy; (2) lower morbidity with vagotomy and gastroenterostomy; (3) vagotomy with gastroenterostomy is a simpler and easier operation; (4) our results with vagotomy with gastroenterostomy are equal to those obtained by gastric resection; (5) fewer permanent sequelae—less diarrhea, anemia, weight loss and "gastric cripples"—following vagotomy with gastroenterostomy, and (6) the larger operation—gastric resection—can always be done later.

Summary

The modified Sippy type of program used in the treatment of duodenal ulcer has been reviewed. Results in 117 patients treated with a new anticholinergic drug (banthine) are given—results which appear favorable. Banthine does not appear to be the answer to ulcer therapy, but it is a valuable adjunct to routine ulcer treatment. New anticholinergic drugs are being studied. Treatment of the major complications of duodenal ulcer is outlined. Results of a two to five year follow-up study on 147 patients on whom vagotomy with gastroenterostomy was performed are reported. Surgery is advised in only 10 to 15 per cent of the patients with duodenal ulcer at the Cleveland Clinic. When operation is indicated it is believed that vagotomy with gastroenterostomy is usually the procedure of choice for duodenal ulcer.

REFERENCES

1. Bockus, H. L.: Gastro-enterology. Philadelphia, W. B. Saunders Co., 1946, vol. 2, p. 318.
2. Palmer, W. L. and Nutter, P. B.: Peptic ulcer and achlorhydria; further study of role of acid gastric juice in pathogenesis of peptic ulcer. Arch. Int. Med. 65:499 (March) 1940.
3. Bockus, H. L., Glassmire, C. and Bank, J.: Fractional gastric analysis in 200 cases of duodenal ulcer. Am. J. Surg. 12:6 (April) 1931.
4. Levin, E., Kirsner, J. B., Palmer, W. L. and Butler, C.: Comparison of nocturnal gastric secretion in patients with duodenal ulcer and in normal individuals. Gastroenterology 10:952 (June) 1948.
5. ———: Nocturnal gastric secretion; studies on normal subjects and on patients with duodenal ulcer, gastric ulcer and gastric carcinoma. Arch. Surg. 56:345 (March) 1948.
6. Vanzant, F. R., Osterberg, A. E., Alvarez, W. C. and Rivers, A. B.: Studies of gastric pepsin; secretion of pepsin in cases of duodenal ulcer and pseudo-ulcer. J. Clin. Investigation 12:557 (May) 1933.
7. Sullivan, A. J. and McKell, T. E.: Personality in Peptic Ulcer. Springfield, Illinois, Charles C Thomas, 1950.
8. Collins, E. N., Pritchett, C. P. and Rossmiller, H. R.: Use of aluminum hydroxide in treatment of peptic ulcer; follow-up study of 246 cases. J.A.M.A. 116:109 (January 11) 1941.
9. Longino, F. H., Grimson, K. S., Chittum, J. R. and Metcalf, B. H.: Orally effective quaternary amine, banthine, capable of reducing gastric motility and secretions. Gastroenterology 14:301 (February) 1950.
10. Grimson, K. S., Lyons, C. K. and Reeves, R. J.: Clinical trial of banthine in 100 patients with peptic ulcer. J.A.M.A. 143:873 (July 8) 1950.
11. Smith, C. A., Woodward, E. R., Janes, C. W. and Dragstedt, L. R.: Effect of banthine on gastric secretion in man and experimental animals. Gastroenterology 15:718 (August) 1950.
12. Brown, C. H. and Collins, E. N.: Use of banthine in treatment of duodenal ulcer. Cleveland Clin. Quart. 17:234 (October) 1950.
13. ———: Use of banthine in treatment of duodenal ulcer. Gastroenterology 18:26 (May) 1951.
14. Scott, L. D. W., Kay, A. W., O'Hare, M. M. and Simpson, J. A.: Hexamethonium bromide in duodenal ulcer. Brit. M. J. 2:1470 (December 30) 1950.
15. Kirsner, J. B., Palmer, W. L., Levin, E. and Klotz, A. P.: Gastric antacid and antisecretory drugs; survey based primarily on their effects upon gastric secretion in man. Ann. Int. Med. 35:785 (October) 1951.
16. Winkelstein, A.: New therapy of peptic ulcer: Continuous alkalinized milk drip into stomach. Am. J. M. Sc. 185:695 (May) 1933.
17. Hoerr, S. O., Dunphy, J. E. and Gray, S. J.: Place of surgery in emergency treatment of acute massive upper gastrointestinal hemorrhage. Surg., Gynec. & Obst. 87:338 (September) 1948.
18. Dunphy, J. E. and Hoerr, S. O.: Indication for emergency operation in severe hemorrhage from gastric or duodenal ulcer. Surgery 24:231 (August) 1948.
19. Woodward, E. R., Harper, P. A., Jr., Tovee, E. B. and Dragstedt, L. R.: Effect of vagotomy on gastric secretion in man and experimental animals. Arch. Surg. 59:1191 (December) 1949.
20. Dragstedt, L. R., Oberhelman, H. A. and Woodward, E. R.: Physiology of gastric secretion. J.A.M.A. 147:1615 (December 22) 1951.
21. Dragstedt, L. R. and Camp, E. H.: Follow-up of gastric vagotomy alone in treatment of peptic ulcer. Gastroenterology 11:460 (October) 1948.
22. Crile, G., Jr.: Surgical treatment of duodenal ulcer: Comparison of results of treatment with and without vagotomy. Rev. Gastroenterol. 17:781 (September) 1950.
23. Collins, E. N. and Stevenson, C. W.: Bilateral vagotomy in treatment of peptic ulcer. Gastroenterology 10:205 (February) 1948.
24. Collins, E. N., Crile, G., Jr. and Davis, J. B.: Follow-up of vagotomy plus gastroenterostomy or pyloroplasty for ulcer. Gastroenterology 11:453 (October) 1948.
25. Collins, E. N., Crile, G., Jr. and Dempsey, W. S.: Medical follow-up of vagotomy plus gastroenterostomy or pyloroplasty for peptic ulcer. Ohio State M. J. 46:33 (January) 1950.
26. Walters, W. and Fahey, M. M.: Vagotomy; immediate results in 28 cases and later results in 68 cases. Proc. Staff Meet., Mayo Clin. 24:501 (September 28) 1949.
27. Hoerr, S. O., Brown, C. H., Rumsey, E. W. and Crile, G., Jr.: Results in treatment of duodenal ulcer by subdiaphragmatic vagus resection with gastroenterostomy: Interim report. J.A.M.A. 149:1437 (August 16) 1952.

Hiatus Hernia

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The majority of hiatus hernias are acquired lesions and are observed in patients of middle age. The symptoms are attributable to the anatomic derangement of the thoracic stomach and the terminal esophagus. Care must be taken to distinguish between complications and symptoms. Therapy, to be successful, must correct the defect by reducing the stomach below the diaphragm. Medical therapy is palliative only; it is indicated when there is relief of symptoms and when there are no complications present.

D. B. EFFLER

HERNIATION of the esophageal hiatus is a common disease in patients of middle age. Contrary to a widespread and unfounded belief, the majority of these herniations are symptomatic and capable of complication. A large percentage of the so-called "chronic dyspeptics" are suffering from symptomatic, unrecognized hiatus hernia. The reluctance of the medical profession to accept this simple entity has been a boon to the manufacturers of proprietary antacids, heartburn emollients and "sour stomach" remedies.

Incidence

Hiatus hernia is usually an acquired lesion. In common with other acquired herniations of the celomic cavity, it occurs most frequently in patients in the middle and older age groups. Efforts to determine its frequency are handicapped by failures on the part of clinicians and radiologists to look for the lesion. Unless the hernia is of unusual size it will be overlooked at postmortem examination; this is particularly true when the autopsy surgeon employs evisceration technics in examining organs.

When specific technics are employed by the radiologist to demonstrate hiatus hernia the lesion will be found in almost 10 per cent of patients undergoing gastrointestinal study. In 1949 Brick[1] reported on 3,448 patients undergoing gastrointestinal barium studies for all types of disease; hiatus hernia was demonstrated in 8.93 per cent of cases. In this same group peptic ulcer was found in 19 per cent of all cases. On the basis of these figures it appears that peptic ulcer and hiatus hernia occur in over 25 per cent of patients whose symptoms warrant upper gastrointestinal investigation.

Classification

Aekerlund, in 1933, offered a simple classification of esophageal hiatus hernias.[2] This classification (Table 1) is based on the anatomic and radiographic appearance of the herniations; in general, it covers all the common types (Figure 1).

Whereas the structural differences that distinguish these three types may seem unimportant, such is not the case. Evaluation of the patient for therapy makes exact diagnosis mandatory; this point will be discussed later.

In addition to the three common types described in Aekerlund's classification, we hear

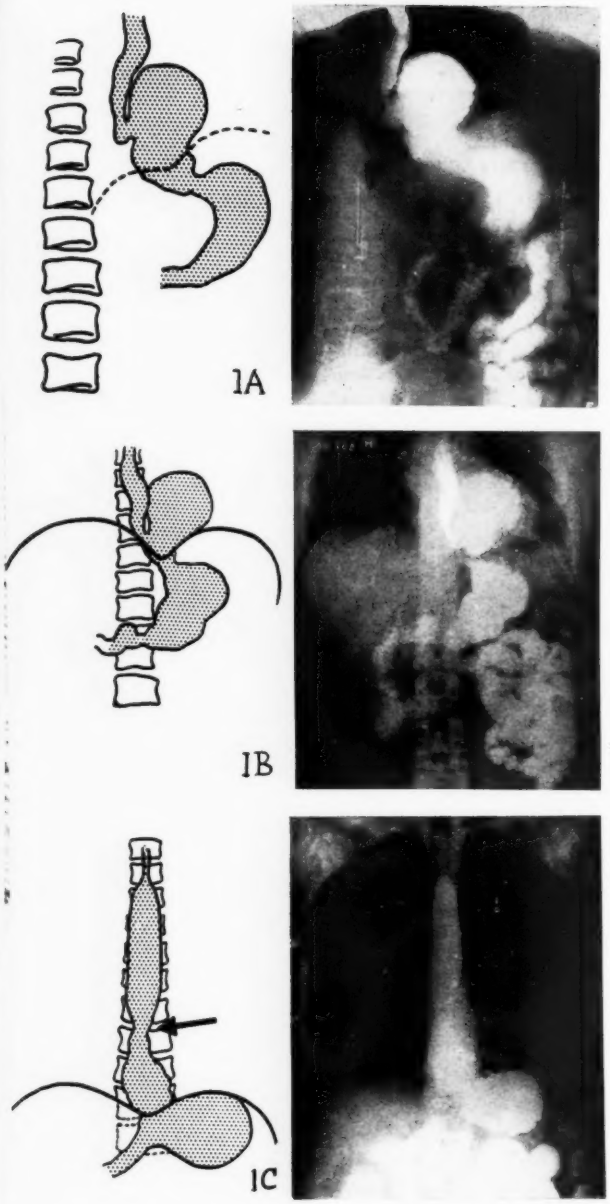


TABLE 1

CLASSIFICATION OF ESOPHAGEAL HIATUS HERNIAS

1. Normal esophagus with pulsion type hernia
2. Normal esophagus with paraesophageal hernia
3. Short esophagus with thoracic stomach

of "reducible" hiatus hernia and "sliding" hernia. The terms reducible and sliding are used by many authors to describe a physical property of the lesion; either the pulsion or paraesophageal type (see Table 1) may possess such mobility. If the thoracic stomach appears to be fixed through all phases of barium studies, the radiologist may speak of "irreducible" hernia. Actually these pictorial terms are descriptive but of little significance clinically or in classification.

Occasionally one sees a more complex picture where all of the stomach is in the mediastinum and several gastric fluid levels appear on the film; or the stomach may be reversed in position with the pylorus and antrum above the diaphragm and the cardia and fundus below. This type is more complex than the simple paraesophageal hernia and merits special reference; since volvulus of the stomach is present and the esophagus is usually of normal length, I use the term "paraesophageal volvulus." Again this is a descriptive term and should not be considered fundamental in classification (Figure 2).

Hiatus hernia is not restricted to the thoracic stomach. Occasionally we see a patient who has a massive herniation with stomach, large bowel, omentum and small intestine occupying the posterior mediastinum. This complicated intrathoracic evisceration merits special consideration; as a working term I refer to this type as a "compound hiatus hernia" (Figure 3).

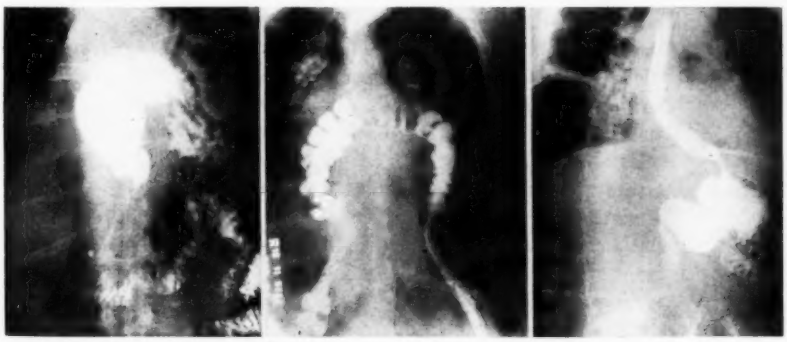
Symptoms

Hiatus hernia may be entirely asympto-

FIGURE 1. Combined radiographic and diagrammatic examples of the three common types of hiatus hernia. (a) Normal esophagus associated with pulsion type hernia. Note that the esophagus enters the thoracic stomach well above the level of the diaphragmatic hiatus. Actually the esophagus is of normal length but is "telescoped" by the herniation. (b) Common type of paraesophageal hiatus hernia with normal length esophagus. The stomach is herniated anteriorly and laterally to the esophagus. (c) True short esophagus with thoracic stomach. In the diagrammatic sketch the arrow indicates the cardiac end of the esophagus. By comparison with the two preceding examples it may be appreciated that the basic problem is entirely different from the ordinary hiatus hernia. Likewise the problem of therapy is considerably altered.

a. b.

FIGURE 2. (a) Unusual type of hiatus hernia with herniation of the pyloric antrum of the stomach; the cardiac and fundic portions are below the diaphragm. This is one type of so-called "paraesophageal volvulus." (b) Total herniation of the stomach producing radiographic evidence of reduplication by volvulus. Note the multiple fluid levels.



a. b. c.

FIGURE 3. Radiographs demonstrating the so-called "compound type of hernia." (a) Radiograph demonstrates almost total herniation of the stomach through the esophageal hiatus. (b) Radiograph illustrating the barium enema in the same patient. The transverse colon has herniated through the large hiatus and is in the posterior mediastinum with the stomach. In addition, operative findings revealed small bowel and omentum within the hernial sac. (c) A barium swallow made one week after transthoracic repair of the tremendous hernia. A stainless steel mesh was employed to reinforce the reconstructed hiatal orifice.

matic and of no clinical significance. When symptoms are present they may vary from mild dyspepsia to severe, unrelenting distress. It should be emphasized that the degree of symptoms cannot be predicated on the size of the hernia or its radiographic appearance. In one patient herniation of the stomach may be an innocuous lesion, its silence broken only by harmless eructation; in another individual a small hernia may produce unrelenting pain, dysphagia or massive bleeding. Symptoms cannot be correlated with the size of the hernia.

Typically the patient with symptomatic hiatus hernia complains of "heartburn" or substernal distress. Usually this symptom appears after eating and is aggravated by lying down. The patient frequently arises during the night, his sleep disturbed by appearance of the heartburn. Relief usually follows self medication with baking soda, proprietary antacids or milk. The recumbent sufferer may be relieved simply by assuming an upright position or getting a glass of water. Some patients will induce vomiting when the distress is accompanied by a "heavy feeling" behind the xiphoid. When the esophagus is short there may be associated dysphagia due to spasm or cicatricial stenosis at the cardia.

Complications

Careful distinction must be made between symptoms and complications in clinical evaluation for therapy. Analysis of the patient's symptoms, coupled with his radiographic studies and physical examination, will assist in the recognition of these complications (see Table 2).

Differential Diagnosis

Symptomatic hiatus hernia is most commonly confused with duodenal ulcer, gallbladder disease, angina pectoris and carcinoma of the cardiac esophagus. The basic

TABLE 2

COMPLICATIONS IN HIATUS HERNIA

1. Bleeding
   a. Occult or massive
   b. Hematemesis or melena
2. Peptic ulcer in thoracic stomach
3. Volvulus with obstruction
4. Stricture (with short esophagus)

clinical differences are enumerated in order:

Duodenal ulcer—The characteristic pain and distress associated with duodenal ulcer occur when the stomach is empty, usually a matter of hours after eating; in hiatus hernia the pain occurs immediately after eating or when the stomach is full. The characteristic distress of duodenal ulcer is usually centered in the midepigastrium or slightly to the right; in hiatus hernia the distress is usually retrosternal and under the left costal margin. Patients with duodenal ulcer may have seasonal variation in their symptoms, whereas the patient with hiatus hernia usually has a constant clinical manifestation of his disease. The radiographic appearance of duodenal ulcer is diagnostic, as is the thoracic stomach associated with hiatus hernia.

Gallbladder disease—In chronic gallbladder disease there is usually the history of colic or intermittent exacerbation of the patient's disease. Colic is rare in the patient with hiatus hernia alone and his symptoms appear almost daily with little variation. The distress of gallbladder disease is characteristically located in the right upper quadrant and referred to the right scapular area. This distribution of pain and discomfort would be unusual when due to hiatus hernia. The patient with gallbladder disease will frequently have intolerance to specific foods, particularly the cabbage variety and fatty types of foods; in symptomatic hiatus hernia all foods may be productive of symptoms and food dyscrasias are usually not significant. Radiographically there is evidence of a nonfunctioning gallbladder or stones, whereas the patient with symptomatic hiatus hernia may have a normal gallbladder study.

Angina pectoris—Hiatus hernia may simulate angina pectoris in many respects. Frequently the resemblance is such as to prompt the diagnosis of "pseudo angina." The patient with angina pectoris will manifest retrosternal discomfort with radiation of his pain to shoulder and arm, usually after emotional excitement or exertion. The patient with hiatus hernia may also have referred pain to his neck and shoulder, probably following the phrenic nerve distribution. Usually, however, this discomfort is exacerbated by meals and recumbency with but little relation to emotional factors. There may be an exertional factor such as lifting or stooping which may aggravate the symptoms of hiatus hernia, probably by increasing intra-abdominal pressure and exaggerating the herniated stomach. Electrocardiographic changes may be of considerable importance in the patient with heart disease, whereas symptomatic hiatus hernia is not productive of such changes.

Carcinoma of the terminal esophagus and cardiac stomach may be present within hiatus hernia but not as a direct secondary disease. In the patient with severe short esophagus that has produced stricture formation of the cardia, a differential diagnosis between carcinoma and inflammatory stenosis may be especially difficult. Esophagoscopy or even exploratory thoracotomy may be necessary to establish the correct diagnosis.

Treatment

Hiatus hernia is a structural disease, and symptoms, when present, are related to the intrathoracic gastric pouch. Permanent reduction of the hernia is invariably followed by permanent relief of symptoms. Selection of therapy must depend on the individual needs of the patient and the degree of discomfort or incapacitation produced by his hernia.

Medical therapy is limited because of the anatomic features of the disease. When symptoms are mild and periodic in nature the conservative measures may suffice. In those patients who have constant distress after a fair trial of medical therapy, surgical correction must be considered. When one or more complications have appeared (see Table 2) the indication for surgical correction is quite clear (Figure 4).

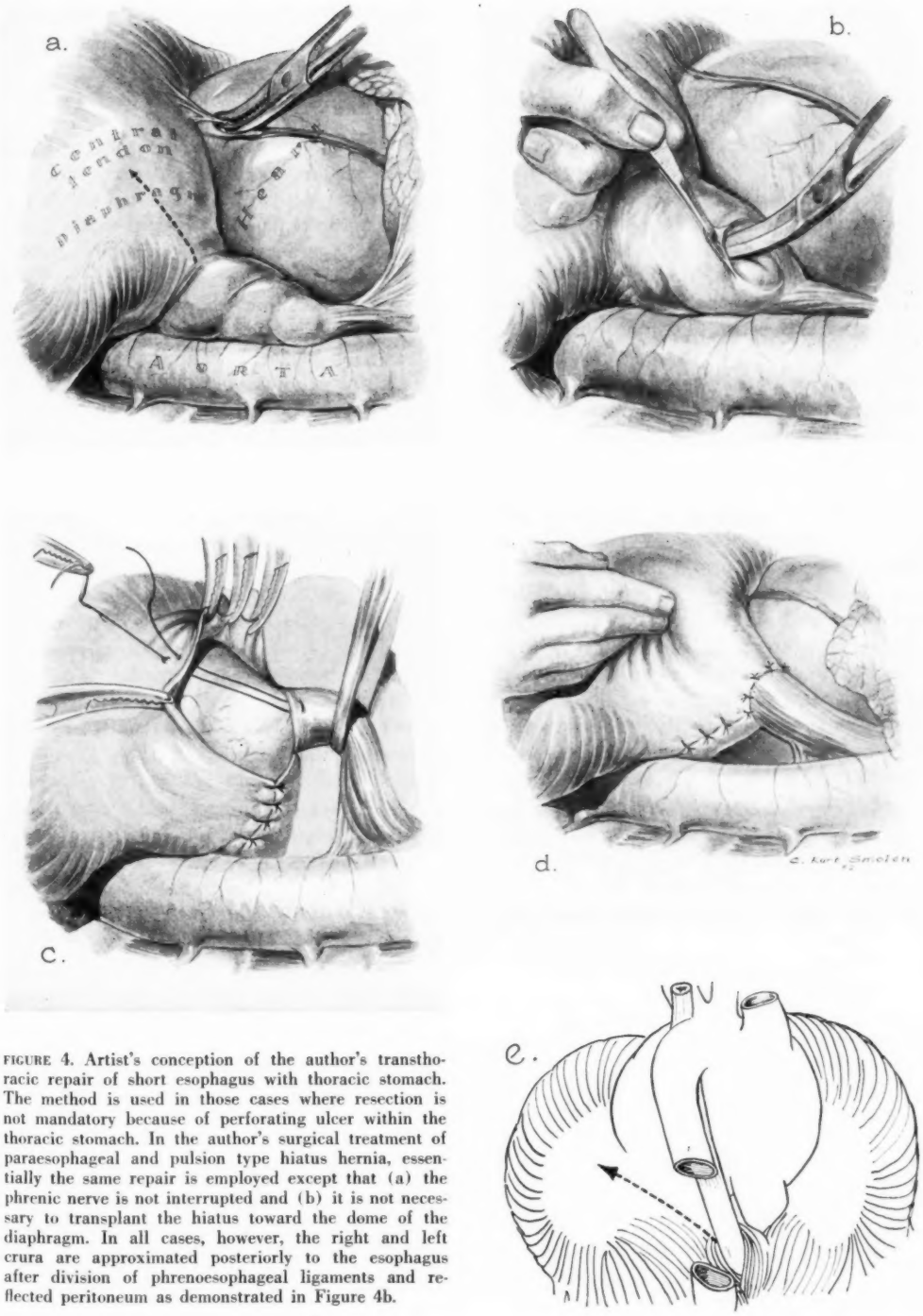


FIGURE 4. Artist's conception of the author's transthoracic repair of short esophagus with thoracic stomach. The method is used in those cases where resection is not mandatory because of perforating ulcer within the thoracic stomach. In the author's surgical treatment of paraesophageal and pulsion type hiatus hernia, essentially the same repair is employed except that (a) the phrenic nerve is not interrupted and (b) it is not necessary to transplant the hiatus toward the dome of the diaphragm. In all cases, however, the right and left crura are approximated posteriorly to the esophagus after division of phrenoesophageal ligaments and reflected peritoneum as demonstrated in Figure 4b.

The hiatus hernia may be approached by either the transabdominal or the transthoracic route. The technic of abdominal correction has been ably described by Harrington[3] and others. I find the transthoracic approach easier, and it offers several distinct advantages: (1) Obesity does not present a hindrance; (2) the anatomic structures are more accessible, and (3) short esophagus, when present, may be correctly treated[4,5] (Figure 4). Under proper conditions the surgical correction of hiatus hernia should be accompanied by a low rate of morbidity. Death should not occur except in severely complicated cases or when heart disease is present. The average period of hospitalization is approximately seven to eight days and ambulation of the patient should begin on the first postoperative day. Before discharge from the hospital it is advisable to secure a postoperative barium study to document the surgical correction of the hiatus hernia. If properly accomplished, the reduction will be permanent and accompanied by a gratifying relief of symptoms. In such cases it is not necessary to continue the patient's medical regimen upon discharge from the hospital. The patient who has no other gastrointestinal disease should be able to partake of a normal diet within a few days after the operation. Additional medications and supplements are neither necessary nor desirable.

Discussion

The symptoms and complications of hiatus hernia are attributable to anatomic derangement of the stomach and terminal esophagus. Successful treatment implies a permanent correction of the defect with complete reduction of the stomach below the diaphragm. Such therapy, when indicated, can be offered with little risk to the patient.

Selection of the patient for surgery must depend on clinical evaluation and on the patient himself. When complications have ensued, or the symptoms are refractory to medical therapy, surgical correction is indicated.

The patient himself should be given an opportunity to voice an opinion in his therapy. Many persons have been prescribed various ulcer regimens and dietary restrictions without relief; to these people the prospect of an unending program of diet, medications and sleeping on an inclined plane is not pleasant. Indeed, the offer of a surgical procedure which combines a high degree of success with a low element of risk may be readily accepted by such a patient.

REFERENCES

1. Brick, I. B.: Incidence of hiatus hernia and associated lesions diagnosed by roentgen ray. Arch. Surg. 58:419 (April) 1949.
2. Akkerlund, A.: Die anatomische Grundlage des Röntgenbildes der sogen: "erworbenen Hiatusbrüche." Acta radiol. 14:523, 1933.
3. Harrington, S. W.: Diagnosis and treatment of various types of diaphragmatic hernia. Am. J. Surg. 50:381 (November) 1940.
4. Effler, D. B. and Collins, E. N.: Complications and surgical treatment of hiatus hernia and short esophagus with thoracic stomach. J.A.M.A. 147:305 (September 22) 1951.
5. Effler, D. B. and Ballinger, C. S.: Complications and surgical treatment of hiatus hernia and short esophagus. J. Thoracic Surg. 22:235 (September) 1951.

POSTGRADUATE COURSES

The following postgraduate courses have been arranged by the American College of Physicians in cooperation with the institutions at which they will be given:

New England Center Hospital and Tufts College Medical School, Boston
Selected topics in hematology, November 10-15; Dr. William Dameshek, director.

University of Illinois College of Medicine and The Presbyterian Hospital, Chicago
Internal medicine: correlation of new and existing basic and clinical factors in diagnosis and treatment, November 17-21; Drs. Frank B. Kelly and Harry F. Dowling, directors.

University of Pennsylvania Graduate School of Medicine, Philadelphia
Gastroenterology, December 1-6; Dr. Henry L. Bockus, director.

University of California School of Medicine, San Francisco
Internal medicine, December 8-12; Dr. Stacy R. Mettier, director.

The Johns Hopkins Hospital and The University Hospital, Baltimore
Recent advances in internal medicine, December 8-13; Drs. Maurice C. Pincoffs and A. McGehee Harvey, directors.

Subdural Hematoma in Infancy

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While subdural hematoma may produce only minimal symptoms in the infant, the lesion is attended by serious consequences in later life. Diagnosis is frequently based on suspicion; confirmation is established by a subdural tap. Therapy consists of repeated subdural taps and excision of the constricting neomembrane. It is important that diagnosis be established and treatment instituted before permanent brain damage occurs.

R. D. MERCER

THE frequency with which subdural hematomas are found in infancy is directly related to the clinician's awareness of the condition. This lesion may be present with only minimal symptoms in the infant but with serious consequences in later life.

The subdural hematoma is essentially a collection of fluid or clotted blood between the dura and the arachnoid membrane covering one or both sides of the brain. The structure of the hematoma varies with the age of the lesion but an essential feature is the tendency for the hematoma to form a membranous sac and for this sac to become filled with a xanthochromic fluid with gradual expansion in size and subsequent compression and atrophy of brain substance.

Frequently the etiology of a specific hematoma is obscure. Trauma seems to be the most important factor with perhaps deficiencies of vitamins K and C, hemorrhagic disease of the newborn and vascular abnormalities playing secondary roles. The frequency of a history of difficulty at birth would suggest that birth trauma is the single most important factor in the production of subdural hematomas.

The use of the words "birth trauma" does not necessarily imply trauma resulting from interference on the part of the physician. On the contrary, such trauma is more apt to occur in the unattended birth, and modern obstetric care with the judicious use of outlet forceps has greatly reduced the incidence of such injuries.

The type of birth injury which is most likely to produce hemorrhage is one in which there have been sudden changes in intracranial pressure or sudden changes in the configuration of the head. Extreme molding of the head of the newborn infant is seldom significant if produced gradually by the forces of labor. Lesser degrees of molding produced rapidly, as in the precipitous delivery, may act as a shearing force and cause tears of the falx, tentorium or pial veins with subsequent hemorrhage. Hemorrhages are also more common in the premature infant, presumably because of the higher incidence of anoxia and the lesser resistance of the capillary walls.

In later infancy, trauma causing subdural hemorrhage may be surprisingly slight. We have seen such an injury following a fall from

a living room couch onto a carpeted floor. In such a case deficiencies of vitamin C and subclinical scurvy may be present.

Recently subdural effusions complicating bacterial meningitis have been described.[1,2] The exact reason for this condition and its relationship to the usual subdural hematoma are not clear. However, the presence of a subdural effusion should be suspected when a patient with bacterial meningitis fails to respond to adequate therapy.

A curious syndrome consisting of multiple spontaneous fractures in association with subdural hematoma has also been described.[3] We are not convinced that this represents a clinical entity unassociated with trauma. However, we have recently seen several infants with this syndrome in whom no history of trauma could be obtained.

The signs and symptoms of subdural hematoma in infancy are varied and it is important to remember that there is no completely characteristic clinical picture.

Ingraham and Matson[4] list the common findings by history and on examination as follows:

History	*Per Cent*
1. Convulsions	55.8
2. Vomiting	47.6
3. Irritability	40.8
4. Infection	39.4
5. Stupor	32.0
6. History of birth trauma	25.9
7. History of other trauma	20.4
Physical and Laboratory Findings	
1. Fever	56.5
2. Hyperactive reflexes	51.7
3. Bulging fontanel	36.1
4. Anemia	31.3
5. Enlarged head	29.2
6. Abnormal fundi	21.8
7. Paralysis	19.0
8. Fractured skull	8.8

Symptoms and Signs

In many instances there are apparently no symptoms during the first two or three months of life. Some patients may have a history of the general symptoms of brain trauma in the neonatal period. These include lethargy and irritability, failure to suck and projectile vomiting. There usually follows a quiescent period before something occurs which brings the patient to the attention of the physician.

The number of infants in whom the chief complaint is failure to gain weight is impressive. This usually becomes evident about the third to the fourth month of life. It is all the more striking since these infants fail to gain in spite of an adequate, or more than adequate, food intake.

A second conspicuous symptom—headache—is not too difficult to diagnose in an infant. Headache is manifested by restlessness, irritability, a worried or pained expression on the face and frequent tossing about and grasping of the head. These infants will also frequently assume a position of opisthotonos, apparently in an effort to gain relief.

As noted, convulsions occur in about half the number of infants with subdural hematomas. These are usually grand mal in character with occasionally a jacksonian component. Convulsions may be the result of damage to the brain in association with, but not necessarily caused by, the subdural hematoma. Not all such convulsions are relieved by removal of the hematoma.

A pseudoceliac syndrome is also sometimes caused by the presence of a subdural hematoma. These infants will exhibit emaciation, a protuberant abdomen and foul, bulky stools. The appetite is usually not impaired. Differential diagnosis must be established between this condition and that of "true" celiac syndrome as well as pancreatic fibrosis and the pseudoceliac syndrome resulting from gastrointestinal allergies.

The vomiting caused by subdural hematomas is not necessarily projectile in nature. The sutures readily separate in these infants and the signs of increased intracranial pressure are not as striking as they are in the older child.

In diagnosing this condition, the most important point to remember is that no abnormality may be encountered on physical examination. On the other hand, there are many suggestive findings which, if present in an infant who is "not doing well," may indicate the presence of a subdural hematoma.

One striking sign is widening of the head

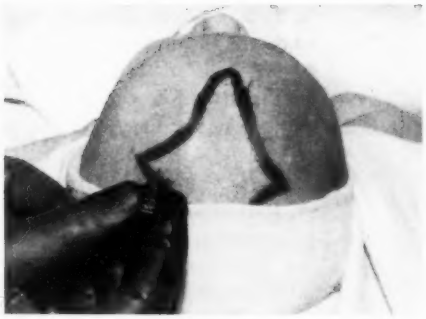

FIGURE 1. Chronic subdural hematoma. Note widening of the head in the parietal diameter.

FIGURE 2 *(right)*. Position of the infant for subdural tap.

in the parietal diameter (Figure 1). The head at first glance may appear hydrocephalic but in most instances of hydrocephalus the head is uniformly enlarged or particularly enlarged in the anteroposterior diameter. In infants with subdural hematomas the head may be normal in the anteroposterior diameter but have a definite brachycephalic appearance from widening in the transverse diameter.

Fever is also a frequent accompaniment. The temperature elevation has no particular pattern and has no relation to infection. Lability of temperature control is apparent and hypothermia may be as striking as the fever.

Changes in the reflexes are usually manifested by hyperactive responses. Occasionally paresis, hemiplegia or paraplegia is demonstrated. When present, such signs are usually indicative of additional brain injury associated etiologically with the subdural hematoma but not necessarily produced by the presence of the hematoma.

Increase in size of the anterior fontanel is frequently present. However, there is such a wide variation in the size of the fontanel in normal infants that only extreme changes should be considered significant. Patients with proved subdural hematomas have been seen with normal or small fontanels.

Increase in tenseness or bulging of the anterior fontanel is a more reliable sign than is increased size. The tenseness of the anterior fontanel should be estimated with the infant quiet and in an upright position. A normal infant may produce bulging of the fontanel by vigorous crying.

Evidence of retinal hemorrhage on funduscopic examination should always arouse the suspicion of the presence of a subdural hematoma. The fundus of an infant is not easy to examine but the procedure can be accomplished with due patience. Mydriatics are helpful but are not necessary. A minimum of difficulty is encountered when an assistant feeds the infant during the examination.

The Subdural Tap

The most important procedure in the diagnosis of subdural hematoma in infancy is to explore the subdural spaces by means of a subdural tap. Electroencephalograms usually fail to demonstrate the lesion. Pneumoencephalograms will usually demonstrate a space-occupying mass but they are unnecessary and subject the patient to unnecessary risk. Subdural tap is a simple procedure which can be performed by any physician who will observe elementary precautions. In the large number of such taps which we have performed, or have seen performed by both experienced and inexperienced individuals, we have never observed a serious complication.

The subdural space is approached through the lateral angles of the anterior fontanel (Figure 2). Even though the anterior fontanel is nearly closed it is frequently possible to introduce the needle through the suture line. There is seldom complete closure of the fontanel in those infants in whom we suspect the presence of a subdural hematoma but if such should be the case, the subdural space should be explored through a burr hole in the temporal region. The best location for such

a burr hole is directly above the external auditory canal.

The site of the subdural tap should be prepared in the ordinary aseptic manner of any surgical procedure. We prefer to cleanse the scalp with soap and water followed by iodine and alcohol. The hair should be cleanly shaved over the puncture site. It is not necessary to shave the head over a wide area for a single diagnostic tap. Undue shaving adds nothing to the sterility of the procedure and introduces an unnecessary psychologic hazard to the parents. However, if the presence of a hematoma is established and frequent taps are contemplated, it is best to shave the anterior half of the head.

The prepared site should be draped with a sterile towel with an assistant firmly holding the head and the drape in position. The head should be on a firm surface such as a thinly padded examining table. The operator should have the outline of the anterior fontanel clearly in mind. It is not necessary to sketch the fontanel as it is illustrated.

The equipment necessary is minimal and readily available (Figure 3). The needle used here is a short beveled number 20 needle fitted with a stylet. These needles are cut down from old spinal puncture needles. The exact size and caliber of the needle are not important. It should, however, have a sharp cutting edge so as to penetrate easily the scalp and the dura. It should also have a short bevel since the normal subdural space is extremely shallow and an attempt is made to avoid penetration of the subarachnoid space or the brain.

The puncture is performed with the needle in the long axis of the patient's body and not directly perpendicular to the skin surface. An attempt is made to get as far away from the midline as possible to avoid entering the superior sagittal sinus. However, it is desirable to keep away from the extreme angle of the fontanel since bleeding may be produced here from rupture of venous spaces near the edges of the bone. The needle is introduced slowly and carefully and a popping sensation is noted as the needle penetrates the dura. This is identical to the sensation which is found in performing a lumbar puncture.

In the normal subdural tap only a few drops of crystal-clear fluid are obtained. Occasionally there will be a drop or two of quickly clotting blood obtained from scalp vessels. When a subdural hematoma is present there is usually a gush of xanthochromic fluid under pressure (Figure 4).

There is no necessity to explore the subdural space blindly with the needle. The great majority of hematomas extend widely over the surface of the brain and there is no doubt of their presence when the subdural space is entered (Figure 5). Occasionally the fluid obtained is no longer xanthochromic but is clear and colorless. Such fluid, however, is usually abundant and of high protein content.

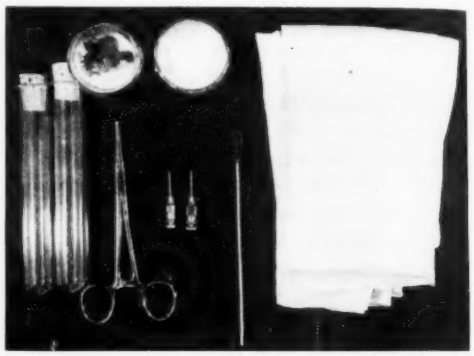

FIGURE 3. Simple equipment necessary to perform a subdural tap.

Clinical Features

The pathologic physiology of the subdural hematoma should make clear certain perplexing clinical features. These are: (1) the frequent long asymptomatic period before any occurrences which bring the patient to the attention of the physician; (2) the apparent periods of exacerbation of symptoms; (3) the presence of fresh red blood cells in what is apparently an old process, and (4) the more serious sequelae, as far as brain damage is concerned, in subdural hematoma of infancy as compared with the same lesion acquired later in life.

The first may be explained by the gradual accumulation of fluid within the membrane of the hematoma due to osmotic forces. Evidently the initial hemorrhage may not be great enough to cause symptoms. The fluid blood then clots and a stage of equilibrium or quiescence occurs. Gradually the clot is organized, partially by fibroblasts growing in from the dura and partially by mesothelial proliferation of the dura itself. The organized clot appears as a sac with a thick-walled outer membrane and a thin-walled inner membrane closely adherent to the arachnoid. In the center of this organized clot a tissue space occurs. The organized tissue of the walls of the sac acts as a semipermeable membrane and the breakdown of old blood provides an entrapped fluid of high protein content and high osmotic pressure. More and more fluid accumulates within this space as a result of osmotic forces until, gradually, the lesion is of sufficient size to cause clinically apparent symptoms.

The walls of the membranous sac of the subdural hematoma contain large capillary spaces. As the sac is stretched these spaces occasionally rupture and there is set up a recurrent cycle of hemorrhage, breakdown of blood, increased osmotic pressure, increased size of the sac and subsequent hemorrhage. This accounts for the periodic exacerbation of signs and the presence of fresh blood cells in an old hematoma.

Cases will be seen where the description given of the pathologic physiology does not hold true. In some cases clotting of the blood never does occur and a membranous sac does not form. In others the initial trauma may produce tearing of the subarachnoid membrane with a flap-valve effect and the subdural fluid will not be xanthochromic and a membrane does not form. These variations in the pathologic process are similar in symptomatology but require some variations in treatment.

Kinley and co-authors[5] have recently thoroughly discussed this variation in pattern and have subdivided this group of cases into subdural hematoma, hygroma and hydroma. They have discussed variations in the surgical technic required by the various types of lesions.

The seriousness of the subdural hematoma in infancy and the urgent necessity for making a diagnosis and instituting treatment are related to the relatively rapid growth of the brain in the first year of life. Nearly half of the postnatal growth of the brain is accomplished by the end of the first year. The presence of a large membranous subdural

FIGURE 4. Xanthochromic fluid removed by diagnostic subdural taps in bilateral chronic subdural hematoma. Note the small amount removed and the sediment of fresh red blood cells in the tube on the right.

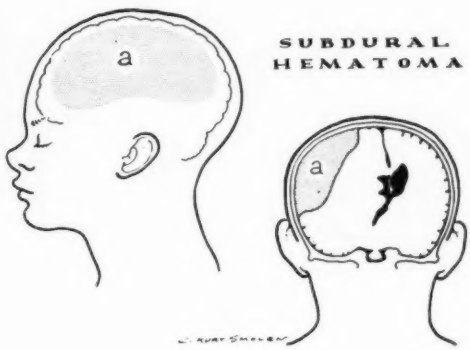

FIGURE 5. Extent of the subdural hematoma. Note compression and atrophy of the brain.

hematoma exerts a constricting force on the rapidly growing brain with the production of brain atrophy and mental retardation.

Treatment

The treatment of subdural hematoma in infancy is surgical and is aimed at, first, relieving the increased intracranial pressure and, second, removing the membrane so that further symptoms do not occur. There is no more satisfying experience in medicine than to watch these acutely ill and apparently hopelessly damaged infants regain their health and weight and change in a matter of weeks from examples of apparent mental retardation to normally functioning children.

The procedure of choice is first to reduce the size of the hematoma by repeated subdural taps. These are performed every other day if the lesion is unilateral, or daily on alternate sides if the lesion is bilateral. When successive taps are contemplated we believe it is wise to place the child on constant antibiotic therapy. No more than 10 cc. of fluid is removed at one time. It is possible to produce acute cerebral edema by rapid removal of a large amount of fluid with the subsequent changes in intracranial pressure relationships. Tapping is continued until the subdural space is nearly or completely dry.

When the subdural space has been dry during two or three repeated taps the patient is ready for surgical exploration. No more than a week should be allowed to elapse between the last subdural tap and craniotomy. Too long a period will allow the reaccumulation of hematoma fluid.

The hematoma membrane is removed through a parietal osteoplastic flap. It is wise to have a polyethylene catheter in place in an ankle vein and to administer blood during the operation. The dura is turned back as a flap with its base toward the superior sagittal sinus. An attempt should be made to effect total removal of the membrane. This is usually extensive and involves the frontoparietotemporal region but seldom extends down over the occipital pole. Since these subdural hematomas are so often bilateral, exploration of both sides is recommended. Kinley advises stripping the inner layer of the dura in those cases of subdural hygromas without the presence of a membrane or with especially thin subdural membrane on the inner surface of the dura. In the subdural hydromas with an arachnoid leak, Kinley advises multiple incisions of the arachnoid over the "lakes" of subarachnoid fluid that are commonly encountered. Follow-up subdural taps should be done to check on the results of the operation. Recurrence of the lesion is not common but occasionally a few cubic centimeters of fluid will collect which can be removed by tapping.

Summary

The etiology and diagnosis of chronic subdural hematoma in infancy are discussed. It is indicated that the diagnosis is frequently based on suspicion and is established by a subdural tap. The pathologic physiology is described to explain certain perplexing features of this condition. Treatment is administered by repeated subdural taps and by the surgical removal of the constricting neomembrane. The rapid growth of the infant brain makes it imperative that this lesion be diagnosed early and treatment established before permanent brain damage occurs.

REFERENCES

1. McKay, R. J., et al.: Collections of subdural fluid complicating meningitis due to *Haemophilus influenzae* (type B); preliminary report. New England J. Med. 242:20 (January 5) 1950.
2. Smith, M. H. D., Dormont, R. E. and Prather, G. W.: Subdural effusions complicating bacterial meningitis. Pediatrics 7:34 (January) 1951.
3. Caffey, J.: Multiple fractures in long bones of infants suffering from chronic subdural hematoma. Am. J. Roentgenol. 56:163 (August) 1946.
4. Ingraham, F. D. and Matson, D. D.: Advances in Pediatrics. Chicago, The Year Book Publishers, Inc., 1949, vol. 4.
5. Kinley, G., Riley, H. J., Jr. and Beck, C. S.: Subdural hematoma, hygroma, and hydroma in infants. J. Pediat. 38:667 (June) 1951.

The Physiology of Ventilation in Chronic Lung Disease

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Pulmonary ventilation represents but one component of over-all pulmonary function which may be affected in various types of chronic lung disease. Since several of the factors responsible for impaired ventilation are of a reversible nature, an understanding of the mechanisms involved is helpful in the rational therapeutic approach to abnormal physiology of chronic pulmonary problems.

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THE physiology of respiration has interested clinicians and investigators for many years, and the processes involved in the normal exchange of oxygen and carbon dioxide between the tissues and surrounding atmosphere are well understood in general. However, the effects of cardiopulmonary disease on the various steps in respiratory gas exchange have been clarified only in the past decade or so. This may be a reflection of the growing list of physiologic methods for evaluation of pulmonary function. Because the heart and lungs function as a unit in the conveyance of respiratory gases between the tissues and external environment, the more widespread use of cardiac catheterization also has added considerably to the current understanding of respiratory physiology.

Pulmonary function is generally accepted as consisting of three essential components: (1) ventilation, or the mass displacement of air in and out of the lungs; (2) alveolorespiratory function, including the diffusion of respiratory gases across the alveolar-capillary barrier and the intrapulmonary distribution of inspired air to functioning alveoli, and (3) cardiopulmonary function, or the relationship between the pulmonary circulation and cardiac performance. Consideration of this latter relationship is essential in the understanding not only of the heart in pulmonary disorders but also of the disturbed pulmonary physiology observed in heart disease.

Even a casual acquaintance with the many clinical and histologic variations observed in diseases of the human lung makes it apparent that one or more of the components of pulmonary physiology may be affected. For this reason physiologists agree that no single pulmonary function test provides an over-all account. Conversely, the most complete physiologic observations do not provide an anatomic diagnosis. The customary clinical, radiologic, pathologic and bacteriologic methods must be utilized to aid in the intelligent interpretation of demonstrable functional alterations. An understanding of the latter, however, may materially assist in the selection of appropriate therapeutic measures.

It is the purpose of this article to consider certain aspects of pulmonary ventilation and the manner in which chronic lung disease may alter this component of respiratory function. Particular attention will be directed to the

effects of (1) obstructive pulmonary emphysema which may occur as a primary disease or in association with many other conditions and (2) pulmonary fibrosis which may be distributed in a variety of patterns depending chiefly on the causative agents. Changes in alveolorespiratory and cardiopulmonary function, which are frequently associated with disturbances of ventilation, will be mentioned as indicated. Reference will be made to certain specific methods of study, but a review of pulmonary function tests will not be attempted. For details of available methods, including the ones to be mentioned here, the reader is referred elsewhere.[1-3]

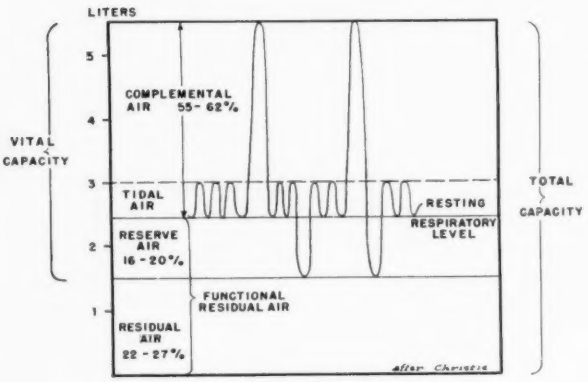

FIGURE 1. Subdivisions of lung volume.

Pulmonary Ventilation

The relatively simple physiologic requirement of ventilation is accomplished only through the integrated performance of a great many structural units, including the various primary and accessory muscles of respiration, the intact pleura, the mediastinum and its contents, the supportive bony framework of the chest and, of course, normally elastic and expansible lungs. Patent air passages are implied, as is a normal stimulus transmitted from the respiratory center, which may be modified by a host of proprioceptive, emotional and other nervous and chemical influences. Disorder of any participating unit is reflected in the amount and form of breathing, as, for example, in bulbar poliomyelitis, pneumothorax, kyphoscoliosis, bronchial asthma or simple anxiety.

The understanding of ventilatory function in any given instance requires the measurement of (1) the lung volume and its subdivisions, (2) the maximum breathing capacity and (3) the state of the minute volume of ventilation at rest and in response to exercise.

The lung volume and its subdivisions—Figure 1 is a diagrammatic representation of the subdivisions of lung volume. The normal values have been shown repeatedly to vary with a number of physical characteristics, including especially age, sex, height and body surface. Numerous tables of expected average values are available, but the regression formulas of Baldwin, et al.[1] for the prediction of both lung volume and maximum breathing capacity have been found to be eminently satisfactory.

The spirographic method is commonly used in the analysis of ventilatory function. Figure 2 is the actual record of a normal subject, as obtained through the use of a recording spirometer with attached ventilometer.* From such a record the resting oxygen consumption and minute volume of ventilation may be calculated, as well as the vital capacity and its subdivisions. The performance of the vital capacity on successive attempts, and the manner of performance of the maximum breathing capacity (maximum voluntary ventilation), may be observed qualitatively as well as quantitatively.

The residual air is the one subdivision of lung volume which must be measured indirectly, usually by the open circuit nitrogen washout method of Darling[4] or the helium dilution method.[5] In the former method, the nitrogen concentration of alveolar air, sampled after seven minutes of pure oxygen breathing, is determined as the "index of intrapulmonary mixing." This value is normally below 2.5 per cent. In the latter method, the helium dilution curve, during seven minutes of closed circuit rebreathing, may be graphically rep-

*Obtainable from the Warren E. Collins Co., Boston, Massachusetts.

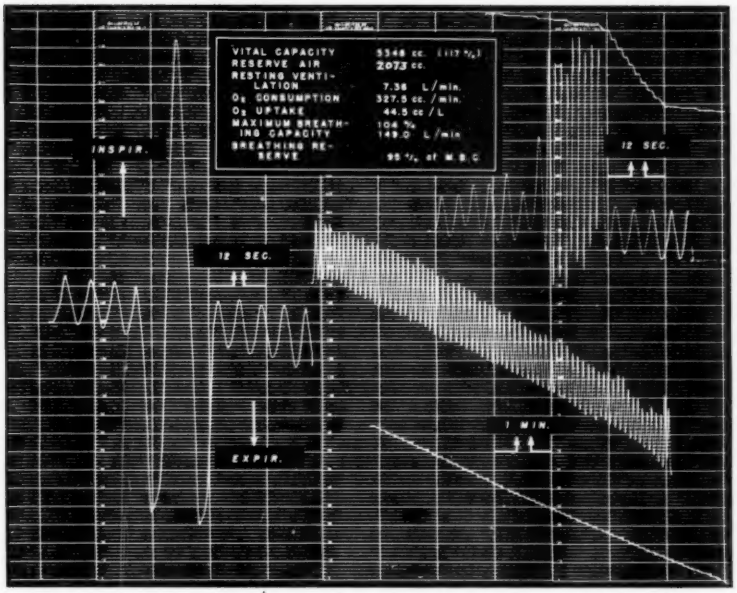

FIGURE 2. Normal spirogram (Case 1). The heavy horizontal lines represent volume changes of 207.3 cc. The vertical lines represent one minute or 12 second intervals, as indicated.

resented to demonstrate the same characteristic (Figure 3).

The maximum breathing capacity is the greatest volume of air that can be moved in and out of the lungs in a given period of time by voluntary effort. It is measured over a 15 or 20 second interval to eliminate the limiting factor of fatigue, and is recorded in liters per minute. The actual quantity is best measured by collecting the expired air in a Tissot spirometer or Douglas bag, where the resistance to breathing is somewhat less than in the recording spirometer. Measurements of ventilation during and after exercise may also be made in this way, and the simultaneous oxygen consumption may be determined by analysis of the collected samples.

Minute volume of ventilation—In a study of pulmonary function the lung volumes are important both as they reflect anatomic alterations and in their relationship to the actual minute volume of ventilation occurring under the conditions of rest, exercise or recovery. The adequacy of a given volume of ventilation not only depends on the variable metabolic state and the fluctuation of the basic chemical and nervous respiratory stimuli but

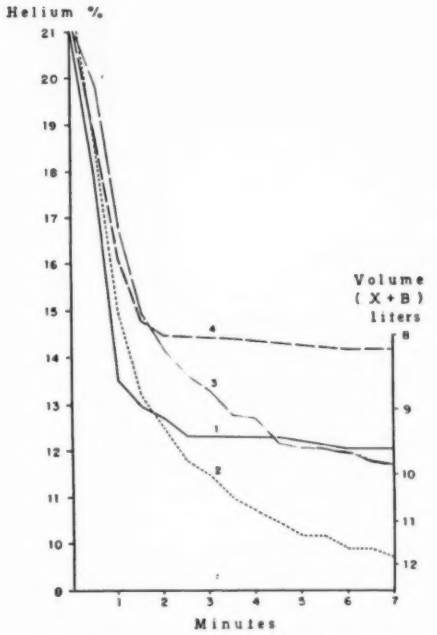

FIGURE 3. Helium dilution curves obtained during residual air determinations in (1) subjects with normal lungs, (2 and 3) emphysema and (4) pulmonary fibrosis. (See Table 1.) (X=Functional residual air, or midcapacity; B=Spirometer circuit volume.)

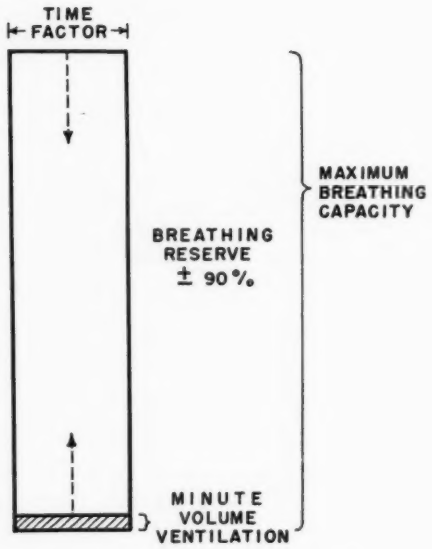

FIGURE 4. The relationship of minute volume of ventilation and maximum breathing capacity to breathing reserve. Arrows indicate the two ways in which breathing reserve may be decreased.

also is related to the relatively fixed residual volume of the lungs which must be diluted with fresh air by each successive inspiration. However, the relationship of the existing ventilation to the maximum ability of the individual to ventilate is found to have a closer bearing on the presence or absence of ventilatory insufficiency. The presence of a time factor in the determination of maximum breathing capacity greatly increases its significance over that of the vital capacity as an index of ventilatory function. As may easily be observed in status asthmaticus, the vital capacity is of little advantage if more than a few seconds are required to produce it.

The relationship of the required minute volume of ventilation to the maximum breathing capacity is presented diagrammatically in Figure 4. The difference between these two quantities, or the breathing reserve, may be encroached upon either by hyperventilation or by impairment of the maximum breathing capacity. Hyperventilation is the most commonly observed alteration of this relationship in the study of normal as well as abnormal persons. It may be the result of abnormal reflex or chemical or emotional stimulation of the respiratory center, but the resting breathing reserve is usually not greatly affected, varying between 95 and 88 per cent of the maximum breathing capacity in the majority of normal individuals. The ventilatory response to exercise has been found to be extremely variable and to depend on the type of exercise test employed as well as on the numerous factors already mentioned. In general, however, the resulting increase in ventilation parallels the carbon dioxide output and, following the standard one minute exercise test described by Baldwin, et al.,[1] the breathing reserve is found to range between 88 and 70 per cent of maximum breathing capacity in the younger age groups and from 75 to 45 per cent in the older age groups.

Ventilatory Insufficiency

In pulmonary disease, ventilation is most strikingly impaired by reduction of the maximum breathing capacity and breathing reserve. This is purely a mechanical disturbance and may result from (1) obstruction of the pulmonary airways and (2) restriction of pulmonary expansion and contraction. When the breathing reserve falls below 60 to 70 per cent of the maximum breathing capacity, dyspnea usually results. Dyspnea has been defined by Meakins[6] as "the consciousness of

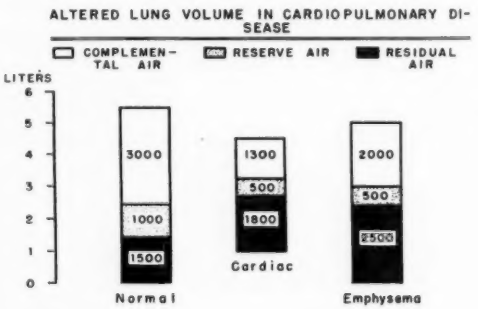

FIGURE 5. Diagrammatic representation of lung volume changes in pulmonary emphysema as compared with those in chronic cardiac decompensation. Loss of pulmonary elasticity and distensibility accounts for the diminished vital capacity and slight increase in residual air of the congested lung.

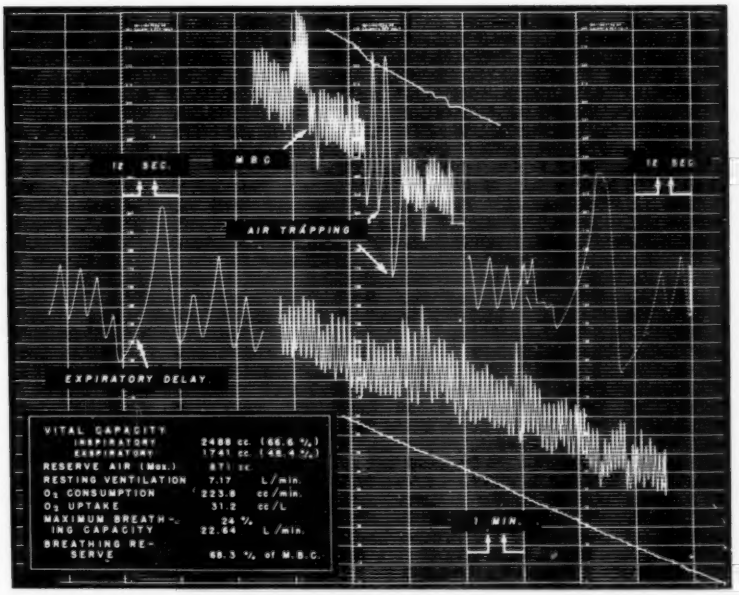

FIGURE 6. Spirogram of Case 2, showing expiratory delay, air trapping and performance of maximum breathing capacity in the inspiratory position.

the necessity for increased respiratory effort." It is, therefore, a purely subjective phenomenon and is difficult, if not impossible, to quantify accurately. However, dyspnea is the chief symptom of ventilatory insufficiency, and in most forms of pulmonary disease is experienced when the patient's ventilatory capacity cannot easily accommodate the actual required ventilation.

In chronic pulmonary emphysema, characteristic changes in ventilatory function occur which are important both in understanding the associated disability and from a diagnostic point of view. The lungs are in a continuous state of relative hyperinflation, and this tendency is reflected not only in the physical and radiologic examination but also in alterations of the lung volume (Figure 5). There may be an increase in the total lung capacity, but of more importance is the absolute and relative increase in the residual air. The vital capacity is usually reduced proportionately, but the reduction bears little quantitative correlation with the degree of disability encountered. The increased ratio of residual air to total capacity results from an inability of the lungs to empty to a normal degree or at a normal rate. This defect is graphically demonstrated in the delayed expiratory curve on the spirogram and the manner of performance of the maximum breathing capacity (Figure 6). The latter is accomplished in the maximum inspiratory position with shallow excursions amounting to 30 per cent of the vital capacity or less, whereas normally the pulmonary midposition is maintained with an amplitude of each breath of about one-half the vital capacity (Figure 2).

Figure 6 is a spirogram of Case 2, a 60 year old engineer with a three year history of progressive exertional dyspnea. Physical and radiologic examination of the chest showed findings characteristic of diffuse obstructive emphysema. The heart and the electrocardiogram were normal, and the arterial blood gas analyses were normal after exercise as well as at rest. The spirogram shows a mild degree of resting hyperventilation with consequent decrease in the oxygen uptake, and a moderate slowing of the expiratory curves. The described alterations in maximum breathing performance are demonstrated, as is the phenomenon of air trapping, or progressively

TABLE 1

PULMONARY FUNCTION DATA IN 4 ILLUSTRATIVE CASES

	CASE 1 (33 year old white male) NORMAL		CASE 2 (60 year old white male) EMPHYSEMA VENTILATORY INSUFFICIENCY		CASE 3 (64 year old white male) EMPHYSEMA VENTILATORY AND ALVEOLORESPIRATORY INSUFFICIENCY		CASE 4 (48 year old white male) BERYLLIOSIS ALVEOLORESPIRATORY INSUFFICIENCY	
	Observed	*Predicted*	*Observed*	*Predicted*	*Observed*	*Predicted*	*Observed*	*Predicted*
1. Lung volumes (cc.)								
Vital capacity	5348	4546	2488	3596	1866	3539	2825	4029
Residual air	1489	1137	5364	1541	3776	1517	1985	1727
Total capacity	6837	5683	7852	5137	5842	5056	4810	5756
$\frac{\text{Residual air}}{\text{Total capacity}}$ (per cent)	22	22	68	30	64	30	45	25
2. Maximum breathing capacity, < minute ventilation, < minute/ m^2 B.S.	149.0	142.7	22.6	93.8	17.9	84.9	93.0	125.5
At rest	3.7	3.6	4.2	4.0	5.0	4.0	5.4	3.8
1 minute standard exercise	9.5	9.0	9.9	11.2	5.6	11.2	18.0	11.1
First minute recovery	9.5	10.0	8.4	14.5	*		18.5	12.6
$\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}}$ (per cent)								
At rest	95	95	68	90	55	90	88	92
1 minute standard exercise	85		26		49		61	
First minute recovery	85		37		*		60	
3. Arterial blood oxyhemoglobin saturation (%)								
At rest		96	97	96	95	96	97	96
First minute recovery		96	97	96	86	96	88	96
Carbon dioxide content, volume per cent								
At rest		48.5	41.9	48.5	52.8	48.5	45.0	48.5
First minute recovery		42.5	46.6	42.5	52.1	42.5	45.0	42.5

*Patient unable to tolerate mouthpiece.

smaller maximal expirations after successive deep breaths. This latter feature of the disability results in a discrepancy between the inspiratory and expiratory vital capacity and reserve air determinations.

The quantitative values obtained in the study of the patient are presented in Table 1, and the helium dilution curve obtained in calculation of the residual air is shown in Figure 3 (Case 2). Not only is the increase in residual air apparent, but the mixing time in the lung spirometer system also is seen to be greatly prolonged. This is a characteristic finding in emphysematous subjects with a residual air of relatively normal size (Figure 3, Case 3) as well as in those with exceptionally large residual volumes. The delayed dilution curve in emphysema results from abnormal intrapulmonary distribution of air associated with structural distortion of the lung, and from the same factors which inhibit the washing out of alveolar nitrogen after seven minutes of pure oxygen breathing in the open circuit method of residual air determination.[7]

The maximum breathing capacity is quantitatively reduced in pulmonary emphysema,

and regularly so to a greater degree than is the vital capacity. This was demonstrated in both Cases 2 and 3 (Table 1), in which the breathing reserve approached the "threshold of dyspnea" even at rest. The reduction in breathing reserve may frequently be contributed to by a variable degree of hyperventilation in all stages of activity, resulting from numerous potential factors including the unequal distribution of air in the lungs previously described, respiratory acidosis and carbon dioxide retention, anoxemia and various neurogenic impulses.

The foregoing alterations of ventilatory function are associated with dyspnea and are the physiologic result of both obstructive and restrictive phenomena occurring in emphysematous lungs. One of the pathologic features of chronic pulmonary emphysema, whether the latter is primary or secondary to other underlying lung disease, is the presence of bronchiolar narrowing. This may occur in more or less widespread distribution and in variable degrees, and is contributed to by accumulated secretions, mucosal edema, thickening of bronchiolar walls and smooth muscle spasm. The inspiratory position of the chest results in maximal dilatation of the narrowed bronchioles, and ventilation proceeds with the least obstruction in this position. Nevertheless the flow of air through partially obstructed bronchioles is turbulent and provides an added resistance to ventilation, thus further increasing the required respiratory effort.

Another essential feature of the emphysematous lung is loss and fragmentation of the normal pulmonary elastic tissue. Thus the tendency of the lung to resume its previous state of contraction following inspiration is lost, expiratory motion is restricted and muscular work is necessary to expel air from the lungs. The shift toward a hyperinflated resting position is enhanced. Subpleural blebs or bullae and large air cysts are not infrequently encountered in chronic emphysema and may communicate poorly or not at all with the tracheobronchial tree.[8,9] They are, therefore, resistant to change in size or shape, and further restrict respiratory movements.

It should be mentioned that not only do these intrinsic changes in chronic pulmonary emphysema increase the work required in breathing, but the associated chest position of hyperinflation has been shown to place the muscles of respiration at a distinct mechanical disadvantage as well. The consequent ventilatory disability of the patient may become extreme.

In addition to these described disturbances in ventilation, impairment of gas exchange or alveolorespiratory insufficiency is frequently present in pulmonary emphysema. The defective exchange of oxygen and carbon dioxide between alveolar air and pulmonary capillary blood has been shown to result chiefly from unequal alveolar distribution of the inspired air, with underventilation of well perfused alveoli.[9] The physiologic manifestation of this defect is arterial oxygen unsaturation, with the superimposed finding of elevated arterial carbon dioxide tension in those instances where compensatory hyperventilation cannot occur because of limited ventilatory capacity.[7] In addition to the defective distribution of inspired air, the mixed venous blood may also be dispersed unequally to the various parts of emphysematous lungs, so that normal perfusion-ventilation relationships are further distorted. The newer technics employed by Riley[10] indicate the presence of a third factor in the production of alveolorespiratory insufficiency, namely, decrease in the oxygen-diffusing capacity of the lung, caused either by a change in the character of the alveolar capillary membrane or by a reduction in the size of the total pulmonary vascular bed.[9]

Pulmonary function data obtained in Case 3 (Table 1) illustrate the changes of alveolorespiratory insufficiency added to those of ventilatory insufficiency resulting from emphysema. Arterial unsaturation and slight hypercapnia were present after exercise, and severe changes in the lung volumes and breathing reserve were apparent. The delayed helium dilution curve encountered during the residual air determination is shown in Figure 3, Case 3.

The most seriously incapacitated group of patients with pulmonary emphysema are those

in whom ventilatory and alveolorespiratory insufficiency is associated with evidence of pulmonary arterial hypertension, polycythemia and chronic congestive heart failure. Severe carbon dioxide retention with respiratory acidosis, arterial anoxia and hypoventilation during all phases of activity characterize this group. The heart becomes involved in such patients because of variable degrees of pulmonary hypertension which in turn results from a number of factors including anatomic restriction of the pulmonary vascular bed, increased viscosity of the blood and increased blood volume due to polycythemia, and pulmonary vasoconstriction caused by anoxia.[11, 12] The hypoventilation in the presence of pronounced hypercapnia and anoxemia is still inadequately explained, but is thought to indicate a profound disturbance in response of respiratory centers to normal stimulation.

The therapy of chronic pulmonary emphysema is largely directed toward maintenance and improvement of the ventilatory capacity. Respiratory infections which may result in increased bronchial secretion, spasm and obstruction must be avoided as carefully as possible, and promptly and vigorously treated if encountered. The continuous use of bronchodilator drugs, especially by aerosol inhalation, is often of dramatic help. Inclusion of penicillin or other antibiotic in the routine aerosol bronchodilator mixture is often indicated by evidence of associated chronic bronchial infection. Occasionally a well fitted abdominal belt is helpful in increasing the vital capacity and maximum breathing capacity, especially if the diaphragm is low and flattened. The use of intermittent positive pressure breathing (inspiratory) in conjunction with the inhaled aerosols containing bronchodilators, wetting agents and antibiotics has recently been reported as effecting striking symptomatic relief in a number of the chronic lung diseases. Improvement in maximum breathing capacity of 25 to 30 per cent has been observed, particularly in cases where emphysema played a major role in the disability.[13]

Oxygen therapy is entirely unnecessary in patients with ventilatory insufficiency alone, and activity need not be restricted. In the cases where alveolorespiratory insufficiency is an additional feature, short periods of oxygen therapy may provide considerable subjective improvement with increased sense of well-being, decreased anorexia and fatigability, and relief of general weakness. However, continuous administration of oxygen should be studiously avoided because addiction is easily acquired. In patients with a tendency to hypercapnia, relief of the anoxic stimulus to respiration may reduce the existing ventilation so as to allow further accumulation of carbon dioxide. Serious depression of the central respiratory impulses has been shown to occur as a result of oxygen-induced carbon dioxide narcosis.[7]

In the group of emphysematous patients having cardiopulmonary insufficiency, additional measures must be employed to combat congestive heart failure. These include digitalis,[14] salt restriction, diuretics and limitation of activity. Since polycythemia and greatly increased blood volumes are almost invariably encountered in this group, the use of repeated phlebotomies is often helpful.[9]

Pulmonary fibrosis may occur in various patterns of distribution in association with nearly every type of chronic pulmonary disease. Pulmonary function may be disturbed in several different ways, depending on the location and character of the fibrosis. As has been shown by Wright and Filley,[15] impairment of ventilation may result for several physiologic reasons: (1) a reduction of the total capacity of the lung; (2) interference with the pumping action of the respiratory apparatus because of increased resistance to bronchial air flow or restriction of the motion of the thoracic bellows, and (3) production of abnormal stimuli arising in the respiratory apparatus and causing hyperventilation via the respiratory centers. Still more profound disturbances in alveolorespiratory and cardiopulmonary function may of course be encountered as a result of interference with alveolar aeration or reduction in size and distensibility of the vascular bed, but the simpler ventilatory disturbances are often found to be of primary functional importance.

Baldwin, et al.[16] described one group of 25 cases of pulmonary fibrosis in which the only demonstrable functional alteration was ventilatory insufficiency. The physiologic findings indicated the presence of persistent hyperventilation, especially during moderate exercise, usually associated with a restriction of lung volumes or of the maximum breathing capacity, or of both. There was no evidence of bronchial obstruction or emphysema, and no associated disturbance of distribution or diffusion of the respiratory gases was discovered. The observed hyperventilation was considered to be due to an increased sensitivity of various reflex respiratory impulses, such as the Hering-Breuer reflex, stimulated by the fibrotic changes in and about the bronchial walls and vascular channels. It was shown not to be a compensating mechanism for abnormalities of distribution and diffusion which might affect the carbon dioxide tension and oxygen saturation of the arterial blood and the acid-base equilibrium. The clinical diagnoses in this group included Boeck's sarcoid, silicosis, radiation fibrosis, bronchiectasis and chronic fibroid tuberculosis. It should be noted that no correlation existed between the severity of the physiologic disturbance and the extent or degree of fibrosis seen on the x-ray films.

The same authors described a second group of 14 patients with pulmonary fibrosis in whom the principal functional disturbance was alveolorespiratory insufficiency resulting in arterial oxygen unsaturation after exercise. This was considered to be the result of the perfusion of large unventilated fibrotic areas of lung, impaired gas exchange across thickened alveolar septums or reduction in total area of the alveolocapillary interface. There was in addition some degree of ventilatory dysfunction manifested by restriction of total lung volumes, relatively normal maximum breathing capacity performed in normal manner, and severe hyperventilation during all phases of activity.

Austrian, et al.[17] have recently described 12 additional patients who manifested these same ventilatory changes and in whom the alveolorespiratory dysfunction was shown to be chiefly the result of interference with the diffusion of oxygen across the alveolar-capillary septum. The term "alveolar-capillary block" was offered to describe this syndrome.[17] The etiologic diagnoses in these 12 cases and the 14 previously mentioned included scleroderma, exposure to sulfur dioxide and asbestos, lymphangitic carcinoma, interstitial pneumonitis, pulmonary granulomatosis following exposure to beryllium, and pulmonary fibrosis and granulomatosis of undetermined etiology.

The data presented by Wright, et al. in a study of pulmonary granulomatosis following exposure to beryllium also were interpreted as indicating alterations in the pulmonary diffusing membrane.[18] Findings in Case 3 (Table 1; Figure 3, curve 4) are presented to illustrate the ventilatory changes of diffuse pulmonary fibrosis, which were in this instance accompanied by disturbance in alveolorespiratory function. This patient was a 48 year old white man who complained of dyspnea on exertion of six months' duration, a moderately productive cough and loss of 10 pounds in weight in three months. His employment for the preceding five years had included intermittent periods during which he worked in high temperatures with various compounds containing beryllium. Physical findings included a moderate hyperventilation at all times, cyanosis after exertion, and distant breath sounds and fine rales at the lung bases. Roentgenograms of the chest showed punctate and streaky infiltration throughout both lungs. A lung biopsy showed focal granulomatosis compatible with berylliosis, and analysis revealed up to 19.2 mg. of beryllium per hundred grams of lung tissue. A skin test was positive for beryllium sensitivity.

Pulmonary function study showed a moderate restriction of the lung volume with maintenance of a relatively normal maximum breathing capacity and hyperventilation in all phases of activity. The helium dilution curve (Figure 3, Case 4) indicated more rapid mixing than is usually seen normally, the final concentration being nearly reached in less than two minutes of rebreathing. There was the additional finding of arterial unsatura-

tion after exercise, indicating superimposed alveolorespiratory disturbance. Cardiac catheterization was carried out and the results indicated a slight degree of pulmonary hypertension and increased pulmonary vascular resistance at rest; these rose further after exercise and were accompanied by an inadequate response in the cardiac output. These findings indicate the presence of early cardiopulmonary insufficiency and were consistent with the clinical observation that pulmonary beryllosis often terminates with the picture of cor pulmonale and right-sided congestive heart failure.

The therapy of pulmonary fibrosis is directed chiefly toward controlling the causative factors, if possible. In most instances prevention of further progress is all that can be accomplished. However, the avoidance or prompt treatment of secondary respiratory infections must be encouraged. Bronchodilator drugs are of little benefit since bronchial narrowing plays a minor role in the disability. Intermittent positive pressure oxygen breathing is rarely of benefit unless a significant degree of emphysema complicates the picture. Occasionally, mild sedation seems to relieve the tendency toward hyperventilation, and exercise tolerance may thus be improved.

In patients with pulmonary fibrosis causing simple ventilatory disturbance, oxygen therapy is unnecessary and activity need not be restricted. In the cases with alveolorespiratory defect, oxygen therapy is frequently helpful, as in pulmonary emphysema. Furthermore, the danger of respiratory depression and carbon dioxide narcosis does not exist in the fibrosis cases, although some tendency to addiction is found. The use of cortisone and ACTH has been reported to be beneficial in some types of pulmonary fibrosis associated with impaired pulmonary gas exchange, particularly in beryllium granulomatosis and silicosis, but further investigation of this therapy is necessary before final evaluation can be made.[19, 20]

When cor pulmonale complicates the terminal phases of pulmonary fibrosis, it requires vigorous and continuous attention. Limitation of activity, digitalization, salt restriction and mercurial diuretics should be employed as in the cases of emphysema with cardiopulmonary insufficiency. The use of phlebotomy again depends on the presence of polycythemia and increased blood volume.

Summary

1. The effects of pulmonary disease on the various steps in respiratory gas exchange have been clarified in the past decade or so, particularly because of improved methods of physiologic study.

2. One of the essential components of pulmonary function which may be affected in chronic lung disease and which may be studied by relatively simple means is ventilation, or the mass displacement of air in and out of the lungs.

3. An understanding of the ventilatory function in any instance requires the measurement of the lung volume and its subdivisions, the maximum breathing capacity (maximum voluntary ventilation) and the minute volume of ventilation required at rest and after exercise. The significance of these determinations is discussed in relation to the concept of breathing reserve.

4. Characteristic alterations in ventilatory function occur in chronic pulmonary emphysema as a result of bronchiolar narrowing and loss of pulmonary elastic tissue. These changes are reviewed and illustrative data presented.

5. Pulmonary fibrosis may be distributed in a variety of anatomic patterns, ventilation frequently being altered as a result of restricted lung volume, impaired pulmonary distensibility and secondary hyperventilation.

6. The ventilatory insufficiency of either pulmonary emphysema or fibrosis of the lungs may be associated with alterations of pulmonary gas exchange due to abnormal alveolar ventilation-perfusion relationships or alterations of the alveolar-capillary membrane, or to both. Pulmonary arterial hypertension and cor pulmonale may also occur. The physiologic significance and therapeutic implications of these additional functional changes are discussed.

References will be included in the author's reprints.

Treatment of Intractable Ulcerative Colitis

GEORGE CRILE, JR.

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When a patient with intractable ulcerative colitis is not benefited by medical therapy, ileostomy and simultaneous colectomy are indicated. There is rarely, if ever, an indication for ileostomy alone. Unsuccessful medical therapy should be discontinued in intractable ulcerative colitis when the patient is not benefited; ileostomy and simultaneous colectomy should be instituted.

G. CRILE, JR.

THE patient I will present is here through the courtesy of Dr. C. Rollins Hanlon. She is a 26 year old married woman who has 2 children and lives with her family and in-laws. She first became ill with ulcerative colitis in 1948 and was admitted to a hospital with complaints of weakness, diarrhea and blood in the stools. A diagnosis of ulcerative colitis was made, and she was given penicillin and streptomycin. Her condition improved and she was discharged two weeks later. Very promptly, however, she was readmitted to the hospital because of recurrent gastrointestinal symptoms.

Concurrently, she developed ulcerations on her legs which were diagnosed as pyoderma gangraenosum. Her second hospital stay lasted two and a half months, during which time she was treated with more drugs, sulfonamides, penicillin and diet, but her status changed very little. She was then transferred to another hospital, where she was given ultraviolet treatment for the ulcer, and a high caloric, high vitamin diet. She improved slowly, and finally the ulcer healed and the disease went into a state of remission. This remission lasted for nearly two years. (To the patient): During that time, Mrs. S., were you able to work and carry on at home quite normally and take care of your children?

PATIENT: Yes, I was.

DR. CRILE: Everything at that time was fine. Were you aware of any particular tensions in your environment to which you might attribute your breakdown? Did anything happen which upset you emotionally, or don't you correlate at all the recurrences of your disease with emotional upset?

PATIENT: There was nothing definite.

DR. CRILE: This patient lives a happy family life, with the possible exception that when both parents and grandparents try to take care of children it always gives rise to some dissension; yet in this case there is no basic conflict in the interests of the four people concerned.

After the two year remission, she had another breakdown and was readmitted to the hospital. (To the patient): Is it true that you have been in and out of the hospital practically all of the time for the last nine months?

Presented at the thirty-sixth (St. Louis) annual Assembly of the Interstate Postgraduate Medical Association.

FIGURE 1 *(left)*. Pyoderma gangraenosum involving the breast. This lesion was enlarging steadily up until the time of colectomy. FIGURE 2 *(center)*. The same lesion as shown in Figure 1, 10 days after colectomy. Note that healing already has begun and the lesion is considerably smaller due to epithelization and contraction. FIGURE 3 *(right)*. The malnutrition of chronic ulcerative colitis. Photograph taken soon after subtotal colectomy with simultaneous ileostomy. The ileostomy is in the right lower quadrant. The stump of the colon is still visible in the central portion of the incision. This will soon retract and heal over completely or leave nothing but a mucous fistula. The lower colon and rectum will be removed at the second operation.

PATIENT: Yes.

DR. CRILE: She has had transfusions, skin grafts to the ulcers on the legs (which have become quite large) and treatment with cortisone and, more recently, with ACTH. The end results of the last-mentioned treatment are not yet apparent because she has just begun this therapy.

(To the patient): You are feeling considerably better, though, at the present time, are you not?

PATIENT: Yes.

DR. CRILE: Your normal weight previously was 100 and you now weigh 87 pounds?

PATIENT: That's right.

DR. CRILE: In other words, we have here the history of a woman who for three years has been in and out of the hospital with ulcerative colitis. One year of the three has been spent in the hospital.

Thank you very much for coming in.

Etiology

What is the etiology of this disease? We hear a great deal about the psychosomatic causes of ulcerative colitis. The patient just presented certainly has a mild background of tension, but most of us have some such situation in our environment. There must be some other factor responsible for the breakdown in this particular case. Is it an infection? Certainly no one has been able to prove the presence of a specific infection; certainly it is not a contagious disease. Is it a deficiency disease? There is no evidence from what we know of the dietary habits of people afflicted with ulcerative colitis that their diets are any different from those of the population at large.

I do not know the nature of ulcerative colitis from the etiologic standpoint. It seems to me to be similar in many respects to what the dermatologists call neurodermatitis, except this disease involves the colon instead of the skin. The same type of person tends to be afflicted by each of these diseases. The outstanding manifestations in each disease are secondary infections which tend to come with

neurodermatitis that is scratched too much, and which occur automatically when the ulcerations in the colon give access to the normal fecal content of the bowel.

Treatment

How are you going to treat a disease when you do not know its origin? That is very difficult. Psychotherapy unquestionably helps, but this is a long, tedious and very expensive process, and generally it is symptomatic treatment, i.e., when these patients are released from the environment of protection which the hospital and the psychiatrist give them, they revert to their disease and their symptoms recur.

Diet is not the cause of ulcerative colitis, and dietary management does not bring about very striking changes in the course of the disease. Blood transfusions and vitamins may be helpful, but in general the vitamin deficiencies and the blood deficiencies continue. It is like pouring the blood through a sieve; there is a constant blood loss, a constant loss of serum proteins. You pour it in, it runs out. The same is true of vitamins. It is very difficult to correct a vitamin deficiency in a patient who has a chronic infection.

Sulfonamide drugs and antibiotics are of symptomatic value in controlling the secondary infection but they do not permanently heal the underlying ulcers. Cortisone is of some value; it makes many patients feel better. ACTH is probably of even more value, and some remissions have been reported following its use. However, many remissions are reported following hospitalization, treatment of almost any kind, or even following no treatment, so it is too early to evaluate the end results of use of cortisone and ACTH except to say that in some cases, in spite of adequate therapy, recurrences occur as soon as the medication is withdrawn, exactly as is the case in arthritis and other conditions in which these drugs are of value.

In the typical case of acute toxic ulcerative colitis the colon is dilated and there is practically no mucosa. It is a shaggy mass of granulation tissue with only shreds of mucosa and muscularis. The inflammatory reaction extends straight through all walls of the bowel, and even the serosa is involved. The lesion in the colon is equivalent to a third degree burn of the skin, and this raw, ulcerating surface is exposed not to the air like a third degree burn of the skin, but to the contents of the colon; it is a third degree burn covered with a fecal poultice.

Do you wonder, therefore, that complications like pyoderma gangraenosum develop? A case of this disease involving the breast is illustrated in Figure 1. It occurs frequently on the extremities but may occur anywhere. In this case there is a large area of pyoderma gangraenosum under the breast, with an undermining, advancing border. The tissues breaking down at the periphery of such an advancing lesion have a violaceous hue and seem to melt away in advance of the progress of the disease.

The same lesion 11 days after colectomy is shown in Figure 2. Note the difference between these two lesions. In Figure 2 it can be seen that epithelization has begun; it is beginning to fill in. The color has changed from violet to brown. This is now a healing lesion. In spite of adequate local care prior to colectomy, this lesion showed no tendency to heal and was advancing steadily. Within 11 days afterward this much healing had taken place, and within a month it was nearly healed.

Another feature of ulcerative colitis which is difficult to handle is that of nutrition. The photograph shown in Figure 3 was taken shortly after subtotal colectomy and ileostomy had been done. The ileostomy can be seen on the right, and the midline mucous fistula of the colon is visible. Within 30 days after removal of the colon this patient gained 30 pounds.

Indications for Surgical Intervention

The majority of patients with chronic ulcerative colitis do well on medical treatment. Most cases are mild and many may be transitory. The disease behaves in many respects like duodenal ulcer in that many patients do extremely well with a little symptomatic treatment; the ulcer heals, the

ulcerative process in the colon subsides and a long remission takes place. There may be an exacerbation at a later date, and again symptomatic treatment is given, but year after year the patients go on and live useful, happy lives.

In cases of duodenal ulcer, the patients who have multiple severe hemorrhages, repeated episodes of pyloric obstruction, perforations, and so forth usually require surgical intervention sooner or later. If they can be handled medically it is perhaps a medical tour de force to avoid a surgical operation, but on the other hand it has done the patient little good if he remains a chronic invalid, loses many days of work and leads a life which he must devote to his ulcer. The same is true in cases of ulcerative colitis. Almost all the patients can avoid operation, but how many of them can do so and continue to carry on their normal activities?

Pyoderma gangraenosum is one indication for surgical intervention in ulcerative colitis. Its presence indicates that you are dealing with a severe form of the disease.

Arthritis probably is another manifestation of the same toxicity. Keratoconjunctivitis may threaten or even cause loss of vision in one or both eyes. These are complications which require prompt intervention lest serious, permanent and irreversible damage is done. The severe wasting shown in Figure 3 is another indication for operation, as is anemia which cannot be corrected by ordinary measures.

Rectal complications and the complex fistulas which may develop as a result of this protracted infection often cause so much discomfort that patients welcome any kind of surgical intervention. Diarrhea may be so severe that the patient literally leads a bathroom life. He cannot go out socially or do his work. He cannot be usefully integrated into the economic system of his home. Thus, diarrhea is another indication for operation when it does not respond to medical treatment.

There is another problem, one which I am not going to emphasize, because no one knows the exact answer to it, namely, the possibility of the development of cancer in some of these patients with severe, chronic ulcerative colitis who go on year after year with the disease. The colon is no exception to the general rule that a large, unhealed ulcer may become malignant. It makes no difference whether it is on the skin as the result of an old burn, whether it is a radiation ulcer or a gastric ulcer—if it goes on year after year unhealed, it leads in many cases to the development of malignancy. Unfortunately, when such cancers occur in the colon, they are of a very malignant type and it is extremely rare that they are recognized and treated in time to enable the patient to be cured of the disease. Fatal cancer develops in perhaps 3 to 25 per cent of patients who have severe, protracted, unhealing ulcerative colitis. I mention those two figures because they are the two extremes in the literature. In our own experience it would seem that, of those patients who have severe ulcerative colitis and who are followed for 5 to 10 years, approximately 5 to 10 per cent develop carcinoma of the colon. I am not referring now to the type of ulcerative colitis which heals promptly with treatment. The situation is somewhat similar to that in cases of gastric ulcer; if the gastric ulcer heals promptly you do not worry about it, and if it goes away altogether and there are no recurrences it gives you no concern. If it persists year after year or does not respond to treatment, on the other hand, then there is something to worry about, and the same is true of ulcerative colitis.

The basic question in considering surgical treatment is whether the patient can make a satisfactory social and economic adjustment to life with his disease. If not, the disease should be removed surgically.

Ileostomy

To illustrate the present day management of ileostomy, I would like to present this young woman, a patient of Dr. R. B. Turnbull of the Cleveland Clinic. She has had an ileostomy and is now wearing an ileostomy appliance. I do not believe anyone in the audience would recognize the fact that this appliance is being worn. These girls can wear bathing suits and indulge in athletics, many of them get

married, and some of them even have children after removal of the entire colon and rectum.

When this young woman wishes to empty the ileostomy bag—which she does two or three times a day—she merely goes to the nearest toilet or sink, undoes the rubber band at the lower part of the bag and empties its contents. It takes no longer than normal bowel habits.

These patients are all intelligent or they would not have developed ulcerative colitis, and almost all of them make satisfactory adjustments mechanically to the ileostomy. Many invent new devices which they promptly patent and begin to sell.

Now we come to the daily care. Once a day this young woman changes her ileostomy bag, which is glued to the abdominal wall. She cleans it off and reapplies it, because the natural desquamation of the skin makes it become loose after a day or so, and most patients change the bag once a day.

In placing the ileostomy, there are certain landmarks which you must avoid. There is absolutely no measurement which you can make geometrically or otherwise to tell you just where to place it. The patient must put on the device before the operation and fit it to herself. She wears the device for a number of hours in all positions and then tells you where it is most comfortable for her. You can no more measure this geometrically—so many centimeters from here to there—than a dressmaker can fit a girl with her best dress by some geometric formula. The ileostomy appliance is something she must wear the rest of her life and she should be the one who is responsible for placing it where it really fits. It must not impinge on the iliac crest nor on the ribs when she bends over.

The glue is easily applied; it is like putting a patch on a tire. The glue is applied to the skin and to the appliance and then, after it is allowed to dry for a minute, the two are put together. After this, the patient will be secure for the next 24 hours.

Another type of ileostomy which we use a great deal is a skin-grafted ileostomy. If an ileostomy is to be satisfactory it must be properly made and, most of all, correctly placed. A point which Dr. Frank Lahey has made is that it should never be placed in the middle of a long scar because when these patients gain weight that scar may become adherent to the fascia and make a groove which will cause the appliance to leak.

TABLE 1

MORTALITY RATE FOR RESECTION OF THE COLON (CLEVELAND CLINIC, 1950)

INDICATIONS	CASES	DEATHS
Cancer	120	0
Diverticulitis	7	1
Ulcerative colitis with ileocolitis	33	2
Miscellaneous	8	0
TOTALS	168	3

The mortality and morbidity rates for ileostomy and colectomy are so low that we should no longer have as our chief objective the avoidance of ileostomy. Rather we should consider the patient as a whole and strive to rehabilitate him to a normal social and economic place in the community.

Acute Fulminating Ulcerative Colitis

The most serious of all complications of ulcerative colitis is the acute toxic or fulminating form of the disease. Our experience indicates that it is in this form of ulcerative colitis that we find the greatest mortality rate today in colonic surgery. Of the 168 patients who underwent resection of the colon at the Cleveland Clinic in 1950, there were 3 deaths; 2 occurred in cases of ulcerative colitis (Table 1). One of these patients had had a perforation of the colon 18 hours before operation; the other was moribund at the time the operation was to be performed.

Acute toxic ulcerative colitis is still one of the greatest single problems in colonic surgery, even though this form of the disease is relatively rare. We have seen only 30 cases in over 600 patients with ulcerative colitis of all types—an incidence of about 5 per cent. These patients have high fever and are desperately ill and extremely toxic. The mortality rate for this group of patients on medical treatment alone formerly was about 30 to 35 per cent at the time of the first hospitaliza-

tion—and that has been about the same regardless of whether they were treated by medical means alone or by ileostomy alone without concomitant colectomy. The worst of it is that whether they have an ileostomy alone or are treated medically, another 30 to 35 per cent of them die after they leave the hospital. These patients are discharged and then, within the next two to five years, even with an ileostomy, exacerbations of the disease occur and they die at home or after readmission to the hospital. So the over-all mortality rate in our hands when these patients are treated by conventional means and followed for a period of from two to five years has been 60 to 70 per cent.

The commonest cause of death in these cases is perforation of the colon and peritonitis. Only 2 of 30 patients with acute toxic ulcerative colitis were rehabilitated socially and economically without a colectomy. Ileostomy alone has no place in the treatment of ulcerative colitis. Colectomy can be done along with the ileostomy with a lower mortality rate than for ileostomy alone, in both chronic and acute cases, because you are not dealing with the contaminated ends of the exteriorized bowel. You do a clean, aseptic operation, removing almost all of the colon right down to the low sigmoid, and establish the ileostomy all at once. If you do an ileostomy first and then a stage colectomy, you always have contaminated ends of bowel, wound infections and the possibility of peritonitis.

Ileostomy alone does not remove the diseased colon, but ileostomy and subtotal colectomy do. With this combination, the portion of the colon which causes the toxicity is removed and at the same time it allows you to tell the patient that if necessary the continuity of the colon could be re-established by anastomosis of the ileum to the stump of the sigmoid. It is not an irrevocable commitment to a permanent ileostomy, because if a cure for ulcerative colitis were devised or if the disease in the rectal stump subsided—which it rarely does—the anastomosis still could be established.

We have operated on 12 patients with acute fulminating toxic ulcerative colitis in the last two years. There have been 2 deaths—a mortality rate of 16 per cent compared with the 60 per cent over-all two to five year mortality rate which attended conservative operation or medical treatment in the past.

We feel that a distended colon or a distended abdomen, with tenderness and evidence of impending peritonitis, is an indication for an emergency operation. We have turned down no one because they were too sick for operation. We have completely revised the old saying that the patient is too sick to be operated on, and we now say that they are too sick not to be operated on. In these fulminating cases the only chance is to remove the colon which is threatening to perforate and which is the cause of the symptoms. Almost without exception, within 24 hours of the time that the major portion of the colon is removed, the temperature starts down and usually within 48 hours or even less the temperature has reached normal and the patient begins to improve. He begins to eat, and remarkable recovery takes place even while he is in the hospital.

Conclusions

1. The mortality of ileostomy and simultaneous colectomy is lower than that of conservative treatment of intractable ulcerative colitis.

2. With the use of the modern ileostomy appliances, the adjustment of the patient to ileostomy is satisfactory.

3. Although most patients do well on medical treatment, unsuccessful conservative treatment should not be prolonged to the point that the patient is denied a satisfactory social and economic adjustment. Ileostomy and simultaneous colectomy may be not only a life-saving procedure but also a personality-saving treatment.

The Management of Patients with Renal Lithiasis

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The management of the patient with renal lithiasis requires the cooperation of the urologist, endocrinologist, chemist and bacteriologist to detect the underlying causes of stone formation and to institute appropriate therapy. Extreme care must be exercised in considering the etiologic factors responsible for stone formation and in planning postoperative management.

C. C. HIGGINS

RECENT progress in the management of patients with renal lithiasis is due not primarily to refinements in operative technic but rather to a clearer concept of the causative factors associated with stone formation. This permits their correction or eradication prior to operation, during the operative procedure or in the period of postoperative observation. There is no single factor responsible for the formation of all stones, and thus all the known causes must be considered. From the standpoint of minimizing the incidence of recurrent stone formation, obviously the etiologic factors must be ascertained in each case. The postoperative regimen for each patient will, of course, differ according to the chemical constituents of the calculus.

The majority of patients with renal lithiasis have experienced a typical attack of renal colic—excruciating pain involving the loin on the affected side and radiating to the genitalia. Unfortunately, 20 per cent of patients with kidney stone have no symptoms referable to that organ but present vague manifestations of gastrointestinal disorder. It is also well to recall that 20 per cent of patients with hydronephrosis have gastrointestinal symptoms. Almost all these patients with renal lithiasis have hematuria, grossly or microscopically. However, in 25 per cent of the cases there will be no gross or microscopic evidence of blood cells in the urine.

In this group of patients, therefore, an initial film of the abdomen and an intravenous urogram should be secured before barium is introduced into the bowel. Otherwise we may obscure a stone in the kidney, a hydronephrosis, or a tumor—in which case the colic is due to the passage of a blood clot down the ureter.

Cabot and Crabtree[1] reported a recurrence of renal calculus or the formation of a new stone in 56 per cent of cases following nephrotomy and in 51 per cent following pyel-

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FIGURE 1. Bilateral renal stag-horn calculi.

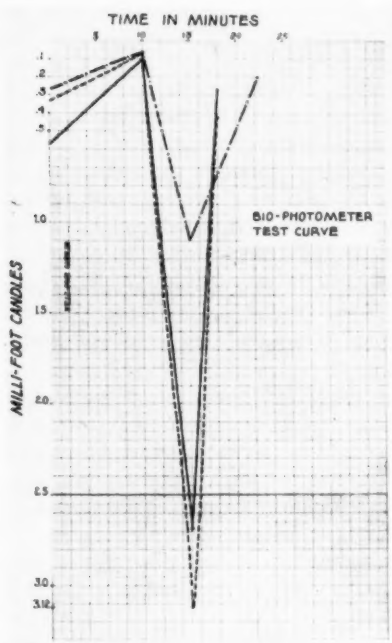

FIGURE 2. Biophotometer test curve.

otomy; Barney[2] reported a recurrence rate of 32 per cent, Herbst[3] 15 per cent and Oppenheimer[4] 14 per cent and 29 per cent. In our series,[5-7] prior to the use of diet in conjunction with other procedures we had utilized in the past, the incidence of new stone formation was 16.9 per cent, and now for over 900 consecutive cases it is 2.4 per cent. Twinem,[8] using the same routine, recently stated that he had reduced the incidence of new stone formation from 28 per cent to 5.3 per cent.

To minimize the incidence of recurrent stone formation, the following factors warrant complete investigation in each case of renal lithiasis:

1. Focal infection. Through the work of Rosenow and Meissner I am convinced that foci of infection, especially in the teeth, the cervix and the prostate, should be eradicated.
2. Local infection in the urinary tract.
3. Coexisting hyperparathyroidism.
4. Is a metabolic disease responsible, such as gout, cystinuria, oxaluria or xanthinuria?
5. If phosphaturia is present, is it (a) temporary as the result of alkaline medication, (b) permanent infective phosphaturia due to the presence of urea-splitting organisms or (c) permanent noninfective phosphaturia associated with diet?
6. Is there an excess of crystalloids in the urine such as may be observed in gout or oxaluria?
7. Are the hydrotropic substances and colloids (such as the 24 hour excretion of urea in the urine) normal?
8. Is there vitamin A deficiency, vitamin B deficiency, or stasis?

Figure 1 is a roentgenogram showing bilateral stag-horn calculi. Seventeen operations had been performed on the kidney of this patient.

Urinary tract infection—Studies which should be made to determine whether there is an infection in the urinary tract include: (1) Gram's stain; (2) culture in glucose-brain broth which is transferred to a blood agar plate; (3) sensitivity test to determine the organism's sensitivity to the newer chemotherapeutic agents; (4) test to establish whether the *p*H of the urine is being shifted

to the alkaline side by the presence of urea-splitting infection. By urea-splitting infection I mean one in which the causative organism has the power to split urea in the urine to ammonia and carbon dioxide with the resultant formation of ammonium carbonate; this combines with the magnesium salts and phosphates to form ammonium magnesium phosphate which is insoluble and which, by rendering the reaction of the urine alkaline, results in the precipitation of the equally earthy phosphates. The chief offenders are *Staphylococcus*, *Streptococcus* and *Proteus* organisms. This shifts the *p*H of the urine to above 5.9 and enhances the precipitation of the alkaline salts.

In a review of 589 cases of lithiasis Rovsing[9] noted that the urine was sterile in 276. Harrington[10] stated that in 480 cases of urinary lithiasis including renal, ureteral and bladder stones he could elicit no evidence of infection in 26 per cent.

We observed that the urine was sterile in 68 of a series of 300 consecutive patients with renal lithiasis; all cases were included in this survey regardless of the size of the calculi. In 500 consecutive cases of recurrent stone formation, in 360 of the bilateral type we found an infection present in 81 per cent; in 140 unilateral cases an infection was present in 26 per cent.

Vitamin deficiency—The results of a biophotometer test are shown in Figure 2; in this case there was vitamin deficiency associated with stone formation, and the curve returned to normal when adequate doses of vitamin A were administered. I do not consider the biophotometer test an accurate one at the present time. Some ophthalmologists may not agree with this, but that, of course, is their privilege. The antimony trichloride test is preferable. About 40 per cent of patients with calculous disease have a positive eye test of vitamin A deficiency.

Hyperparathyroidism — Hyperparathyroidism is the causative factor in the production of kidney stones in approximately 4 to 5 per cent of cases. It is stated frequently that a study of the blood calcium and the blood phosphorus suffices to make an accurate diagnosis. This is not true. Fluctuations in the blood calcium occur in response to fluctuations in the total proteins of the blood in order to maintain a constant calcium ion concentration. The calcium ion concentration is therefore dependent on the equilibrium between the calcium in the blood and the proteins. We should determine the calcium ion concentration, which consists merely of blood calcium, and total protein, by using the chart of McLean and Hastings[11] (Figure 3). We have not found any evidence of changes in the hydrogen ion concentration with other bone diseases. Obviously, if an adenoma of the parathyroid gland is present it must be removed.

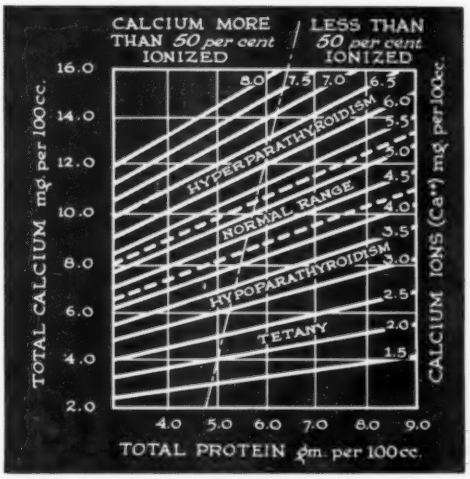

FIGURE 3. Chart for determination of calcium ion concentration. (McLean and Hastings.[11])

I operated on a patient about 15 years ago and removed a stone from the right kidney. At that time there was no evidence of bony changes. The patient returned later and it was found that he had a stag-horn stone in the right kidney and definite bone changes compatible with a diagnosis of hyperparathyroidism (Figure 4).

Stasis—The question arises, does the stone precede the stasis or does stasis occur prior to the formation of a stone? Figure 5 is a roentgenogram of a patient with left hydronephrosis. She complained of gastrointestinal symp-

FIGURE 4. Hyperparathyroidism and renal lithiasis.

toms and I advised a plastic operation on the kidney pelvis. This was refused. She returned two years later; the gallbladder and the appendix had been removed without relief of symptoms. A film taken at that time showed a stone in the kidney (Figure 6). The calculus was removed and a plastic operation was performed on the kidney pelvis. Intravenous urograms should be secured routinely before operation, and if stasis is demonstrable it may be corrected at operation.

Types of Calculi

The chemical constituents of renal calculi vary greatly. Figures 7 through 10 illustrate various types.

Oxalate calculus—Ordinarily about 18 to 30 mg. of oxalate is excreted in the urine daily. In one of our cases, this amount was over 50 mg. (Figure 7).

Cystine calculus—Cystinuria is a disease of intermediate protein metabolism in which cystine may be found in the urine partly in solution and also in crystalline deposit. Under normal conditions cystine is oxidized completely and the sulfur is excreted as sulfate. Cystinuria is a familial disease, and more than one member of a family usually will be found to have a cystine calculus (Figure 8). The stone is amenable to dissolution by dietary means. Of all persons with cystinuria, 2.5 per cent will develop a renal calculus.

Uric acid calculus—One of our patients (roentgenogram shown in Figure 9) had symptoms which were gastrointestinal in type.

FIGURE 5. Left hydronephrosis.

FIGURE 6. Same patient as Figure 5; later roentgenogram revealing the formation of a calculus.

FIGURE 7. Renal lithiasis—right oxalate calculi.

FIGURE 8. Cystine renal calculus.

FIGURE 9. Left renal calculus—uric acid type.

The gallbladder and the appendix were removed, but the symptoms recurred postoperatively. There were no blood cells in the urine. A pyelogram showed a nonopaque stone not visualized on the initial film. The stone was removed and proved to be a uric acid calculus. The patient's symptoms were relieved.

It is well to recall that a patient may develop a uric acid calculus and have an elevated blood uric acid level without any other clinical manifestations of gout. Normally a man excretes 0.2 gm. to 1.5 gm. of uric acid daily; this amount is influenced chiefly by exogenous sources.

Xanthic calculus—Xanthic stones are a more unusual type of renal calculus. They are clearly shown when air is injected into the renal pelvis (Figure 10).

Uric acid is the most important purine excreted in the urine. However, 30 to 50 mg. of the purine bases—xanthine, hypoxanthine, adenine and guanine—is excreted daily. Matthews[12] estimated that 16 to 60 mg. of purine base is eliminated daily in the urine.

FIGURE 10. Xanthic calculus, upper calyx right kidney (air pyelogram).

Surgical Procedures

I will not go into detail concerning the surgical procedures utilized in calculous disease except to say that conservatism is essential. In 16 per cent of cases, a patient with a stone in one kidney will have an attack of colic in the opposite side within less than three years.

The majority of calculi can be removed by a simple linear incision in the kidney pelvis, and if there is a stag-horn stone and good renal parenchyma there should be no hesitancy in splitting the kidney in half, removing the stone and resuturing the kidney. To reiterate, conservative treatment is of paramount importance.

Postoperative Care

The following measures are routine in the care of patients following surgical removal of renal calculi: (1) Abundant fluid intake—for one year we have the patient drink distilled water; (2) elimination of stasis; (3) eradication of local and focal infections; (4) correction of metabolic errors; (5) removal of an adenoma of the parathyroid gland (if one is present); (6) large doses of vitamin A for specific healing effect on epithelial structures or for correction of vitamin A deficiency; (7) correction of vitamin B deficiency for its effect on oxaluria; (8) dietary adjustment.

In the use of diet in treatment of renal lithiasis, two facts should be remembered: (1) One group of stones—phosphate and carbonate—can form only in urine which is alkaline and (2) cystine, uric acid, xanthic and guanine stones are produced from salts which precipitate in urine which is acid. Oxalates are precipitated in connection with a wide range of urinary *p*H and must be treated a little differently.

Figure 11, for example, is the chart of a patient who had had three operations during a period of 18 months for stone in a kidney. As might be expected, the *p*H of the urine on the affected side, the right side, was 7.9. Chemically, therefore, this stone was composed of phosphates or phosphates and carbonates. The patient was placed on a high vitamin A, acid-ash diet to shift the *p*H of the urine down to a point where phosphates and carbonates are maintained in complete solution. In this instance the *p*H was reduced to 4.4 and 4.6, at which point the patient was precipitating uric acid from both kidneys and was a potential candidate for a uric acid stone instead of a phosphate calculus. By further adjustment of the diet we found that at a *p*H of 5.2 in this patient all the salts are maintained in complete solution and it is chemically impossible that the patient will develop another stone.

The opposite picture is illustrated in Figure 12. The urinary *p*H in this patient was 4.9, at which point uric acid first precipitates. The patient was placed on an alkali-ash, low purine diet and the *p*H was shifted up toward the alkaline side to a point where the uric acid is maintained in complete solution. Still the *p*H is below the point at which he would precipitate phosphates and carbonates.

What do we do with a patient with a *Proteus* infection in whom the *p*H cannot be shifted to the acid side by dietary means? The *Proteus* organism is not sensitive to any of the newer drugs. This patient is placed on AMPHOJEL® or BASALJEL® as would be done in a case of duodenal ulcer. A normal person will excrete 1 gm. of phosphates daily in the urine. The aluminum gel passing through the gastrointestinal tract unites with the phosphates, forming insoluble aluminum phosphate which

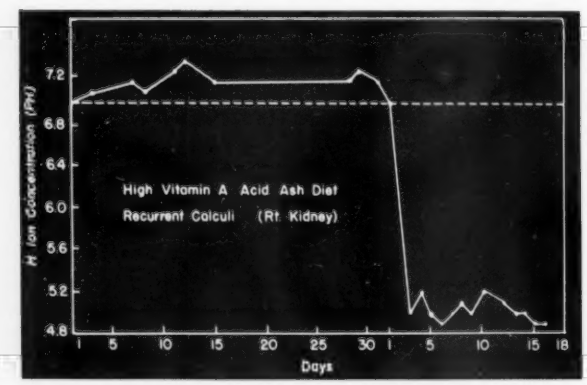

FIGURE 11. Curve of urinary *p*H.

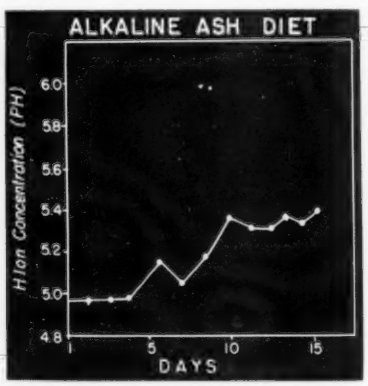

FIGURE 12. Curve of urinary *p*H.

is excreted unchanged in the bowel. This minimizes the resorption of phosphates from the bowel itself and promotes more complete tubular resorption of phosphates in the kidney. We thus divert the excretion of phosphates from the kidneys to the bowel. Practically all the phosphates can be removed from the urine, but it might not be safe to do so. We may reduce the phosphate excretion in these patients from 600 mg. to about 150 or 200 mg., at which point they can be maintained indefinitely. This is the only type of treatment that can be used in instances of an alkaline stone in which the *p*H of the urine cannot be controlled by dietary means (Figure 13).

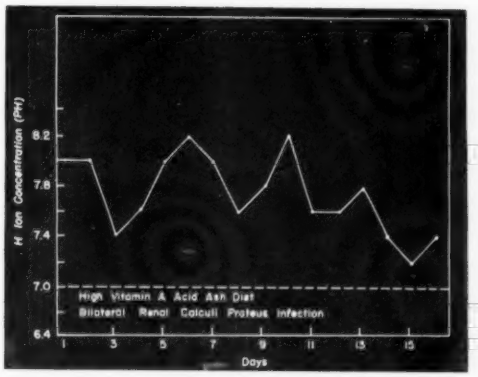

FIGURE 13. *Proteus* infection; inability to control *p*H of urine.

Another type of treatment, one which is in a more experimental stage, is the use of estrogens.[14] This method is based on the concept that citric acid excreted in the urine is not a waste product but rather a valuable constituent of the urine by virtue of its capacity to enhance the solubility of calcium. By use of estrogens we increase the excretion of citric acid and decrease the excretion of calcium. I have used this treatment only in women beyond the age of menopause, because if they still have menses you may provoke intermenstrual bleeding, and in men, of course, it causes impotency.

Figure 14 shows a cystine stone in the right kidney. The patient was placed on a low purine, alkali-ash diet which converts the urine from acid to alkaline. In Figure 15 it is seen that the stone has undergone fragmentation, and Figure 16 shows that the calculus has been completely dissolved.

Patients for whom we prescribe the diet are given a *p*H apparatus and make their own

FIGURE 14. Cystine stone, right kidney.

FIGURE 15. Same patient as in Figure 14; stone undergoing fragmentation.

FIGURE 16. Same patient as Figures 14 and 15; stone completely dissolved.

FIGURE 17. Nephrocalcinosis.

urine determinations, presenting these to their physicians at monthly intervals.

Nephrocalcinosis

A condition which appears to be increasing in frequency in this country is so-called nephrocalcinosis, a diffuse calcification involving the renal parenchyma of both kidneys, chiefly the pyramids (Figure 17). There are associated blood chemistry changes consisting of hyperchloremia and acidosis, and also changes in the calcium metabolism.

Early in the course of the disease there may be no clinical symptoms, and the finding of a renal calculus is accidental. Later the patient complains of weakness, nausea and vomiting, polyuria and polydipsia. Occasionally the first complaint will be an attack of renal colic when a stone in the papilla ulcerates through the kidney pelvis. The disease may be observed in children or adults.

That it is not a disease of the glomeruli of the kidney is indicated by a normal inulin and urea clearance and a normal blood urea level. That the proximal tubules of the kidney are not involved is indicated by the absence of glycosuria, a normal DIODRAST® clearance, and a negative phenolsulfonphthalein function test. That it is a disease of the distal convoluted tubules is indicated by the patient's inability to concentrate urine, the constant presence of acid urine, and the presence of a systemic acidosis.

Treatment—In treating nephrocalcinosis we attempt to (1) correct acidosis, (2) reduce hyperchloremia and (3) correct the negative calcium balance by promoting better absorption of the calcium and reducing the hypercalcinuria. This is accomplished by use of a citric acid mixture containing 140 gm. of citric acid and 98 gm. of sodium citrate in 1000 cc. of water; approximately 60 cc. is taken daily. Also, the salt in the diet is reduced and the patient is given additional amounts of vitamin D.

The question arises whether it is entirely coincidental that the increase in the incidence of nephrocalcinosis corresponds chronologically to the introduction of the sulfonamide drugs. Seven of the first 10 patients we observed (reported by Engel[13]) had taken sulfonamides over long periods of time. I do not wish to imply that this is the only cause of injury to the distal convoluted tubules because we know this is not true. It does, however, indicate that there may be some danger in the extended use of sulfonamides.

REFERENCES

1. CABOT, H. and CRABTREE, E. G.: Frequency of recurrence of stone in the kidney after operation. Surg., Gynec. & Obst. 21:223-225 (December) 1915.
2. BARNEY, J. D.: Recurrent renal calculi. Surg., Gynec. & Obst. 35:743-748 (December) 1922.
3. HERBST, R. H.: Recurrent renal calculus; its cause and prevention. Am. J. Surg. 12:58-62 (April) 1931.
4. OPPENHEIMER, G. D.: Nephrectomy versus conservative operation in unilateral calculous disease of upper urinary tract. Surg., Gynec. & Obst. 65:829-836 (December) 1937.
5. HIGGINS, C. C.: Renal Lithiasis. Springfield, Illinois, Charles C Thomas, 1943.
6. ———: Etiology and management of renal lithiasis. J. Urol. 62:403-409 (October) 1949.
7. ———: Etiology and prevention of renal calculi. Tr. Am. A. Genito-Urin. Surgeons, 1951.
8. TWINEM, F. P.: Study of recurrence following operations for nephrolithiasis. J. Urol. 37:259-267 (February) 1937.
9. ROVSING, T.: Ueber Diagnose und Behandlung der Nierensteine auf Grund neunundzwanzigjahriger Erfahrungen. Ztschr. f. urol. Chir. 12:358-384 (March) 1923.
10. HARRINGTON, H. L.: Clinical study of 480 cases of urinary lithiasis. J. Urol. 44:507-519 (October) 1940.
11. MCLEAN, F. C. and HASTINGS, A. B.: Clinical estimation and significance of calcium ion concentration in blood. Am. J. M. Sc. 189:601-613 (May) 1935.
12. MATTHEWS, A. P.: Physiological Chemistry. Ed. 5. New York. William Wood and Company, 1930.
13. ENGEL, W. J.: Nephrocalcinosis. J.A.M.A. 145:288-294 (February 3) 1951.
14. SHORR, E.: Possible usefulness of estrogens and aluminum hydroxide gels in management of renal stone. J. Urol. 53:507-520 (April) 1945.

Diseases of the Gallbladder and Biliary Tract

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Although the clinical diagnosis of gallstones is especially accurate today, occasionally there are poor results after cholecystectomy for stones. The commonest causes of dissatisfaction are (1) attributing symptoms actually due to other conditions to the gallbladder and (2) overlooking the existence of stones in the common duct. Routine operative cholangiography offers an efficient means of detecting common duct stones.

S. O. HOERR

At present, the diagnosis of gallstones is very accurate, thanks to a better understanding of the clinical manifestations and in considerable measure to the Graham-Cole test. Also, we have a satisfactory treatment for gallstones in cholecystectomy, so that for a simple, uncomplicated removal of the gallbladder the operative risk is 1 per cent or less.

Alternative methods of treating gallstones are not yet practical. It has been suggested that stones might be dissolved by supersonic waves, and one of my colleagues was prompted to say that the medical profession has tried to treat many diseases with "sound waves" but gallstones is one that has not yet responded to this form of treatment.

I wish to present a patient who demonstrates some of the salient points in diagnosis and treatment of gallbladder disease. This patient, who was recently operated on at one of the St. Louis hospitals, is a 54 year old widow with 3 children. In January 1951, she had a mild attack of pain which began in the epigastrium and spread to the right side and was associated with nausea and vomiting. She consulted a physician, and it was thought that she had a virus infection. No opiates were required for relief of pain, and she was given penicillin. Several weeks later she experienced a similar attack, again not very severe, associated this time, however, with jaundice. She noted that her stools were light and her urine was dark. The jaundice faded after a few days and she felt pretty well. A month or two later she again had an attack of pain associated with nausea and vomiting. (To the patient): You itched intensely?

PATIENT: I did.

DR. HOERR: She also had chills and fever. The jaundice again was transient in character and disappeared. In between these attacks you felt perfectly well?

PATIENT: Yes.

DR. HOERR: In June she had another attack, again became jaundiced, but this time the jaundice did not disappear. In August there was an exacerbation of the pain and in September she was admitted to the hospital. Physical examination at that time disclosed

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a jaundiced lady in no particular distress. You weren't having any pain at that time?

PATIENT: No, I wasn't.

DR. HOERR: What about various foods? Did they all agree with you?

PATIENT: They all agreed with me.

DR. HOERR: What about fatty foods? Could you eat them while you were jaundiced?

PATIENT: Not too well.

DR. HOERR: There had been an episode between 1944 and 1949 when she apparently had a mild diabetes. She took an unknown quantity of an insulin preparation, dieted, lost weight, and in 1949 it was considered unnecessary to continue the insulin.

In addition to the jaundice, physical examination at the time of admission to the hospital revealed the liver to be palpable several inches below the costal margin—a finding which is quite characteristic in patients with obstructive jaundice of any duration. She was carefully studied from a laboratory standpoint, and it was found that her serum proteins were normal and that her serum bilirubin was five or six times the normal level (between 5 and 6 mg. per cent). Serum amylase was normal, and the cephalin flocculation test was negative. She had a slightly elevated thymol turbidity test and a definitely elevated alkaline phosphatase.

Complete study of the gastrointestinal tract was done, and the diagnosis of gallstones with common duct stone and obstructive jaundice was established. It was reassuring to have a normal x-ray of the stomach and duodenum, because occasionally there may be carcinoma of the stomach which has spread, causing a metastasis and blockage of the common duct. A roentgenogram of the colon was likewise normal.

On September 20 she underwent operation and a fistula was found between the gallbladder and the common duct—quite an unusual finding. Two common duct stones were found blocking the distal end of the common duct. The stones were removed, the gallbladder was removed and a T tube was placed in the common duct. A postoperative cholangiogram showed fairly satisfactory filling of the biliary tract—at least no disquieting, large radiolucent shadows representing residual stones.

Since her discharge she has done beautifully and I think she is going to have an excellent result.

Diagnosis

The clinical diagnosis of gallstones can be very accurate if there is typical biliary colic. A typical attack comes on very suddenly—the patient is well one minute and overcome with severe pain the next. The pain starts either in the epigastrium or in the right upper quadrant and frequently radiates to the tip of the scapula or to the center of the back. In such an attack, particularly when its severity can be gauged by determining whether opiates are necessary to relieve the pain or by establishing that the pain is as severe as others that the patient has had—such as that of labor and childbirth—we know we are dealing with acute biliary colic. If such an attack is associated with jaundice the diagnosis becomes almost 100 per cent certain from a clinical standpoint.

If an attack of colic progresses to acute cholecystitis, there may be the additional findings of tenderness, percussion tenderness in the right upper quadrant, sometimes a palpable tender mass or a palpable gallbladder.

The distinction between gallstone colic and acute cholecystitis is sometimes extremely difficult to make. Probably most acute cholecystitis begins as an obstruction from a stone trying to pass, with typical colicky pains. If this pain persists for longer than a few hours, it is probably safe to assume that we are dealing with acute cholecystitis.

Far less reliable than colic is so-called biliary dyspepsia. Patients with this symptom are those who cannot look a pork chop in the face, have trouble with onions, cabbage, raw apples, pastry, and so forth. It is true that such digestive disturbances may exist in cases of gallstones; unfortunately, it is also true that these patients sometimes have exactly the same symptoms after removal of the stone-filled gallbladder. In these cases we require further evidence to make a diagnosis of gallstones, because this type of digestive disturbance may be produced by a duodenal

ulcer, by cirrhosis of the liver and to some extent by the irritable colon syndrome.

Roentgenograms may be extremely helpful. When stones are visible on the plane film they may be completely diagnostic. Unfortunately, only 10 to 20 per cent of all gallstones have sufficient calcium in them to cast a shadow. However, if the gallbladder will fill on cholecystography, often the radiolucent shadows of either small or large stones can be seen, making the diagnosis 100 per cent certain.

Pitfalls in interpreting cholecystograms—When we encounter the nonfilling gallbladder by cholecystography (and I have deliberately used the word "nonfilling" rather than "nonfunctioning") the situation may be somewhat misleading. The following factors must be considered: (1) Make sure the patient takes the dye. Occasionally, in spite of all instructions, patients do misunderstand. I remember one patient who was instructed to take anal suppositories and was very surprised and delighted with the results she got after she removed the silver paper they were wrapped in; she had failed to do so prior to that time and had not experienced the expected relief.

(2) Make sure the dye stays in the stomach. Some patients become nauseated and vomit the dye, and of course an interpretation based on such a test will be fallacious.

(3) Is the stomach obstructed? The test is almost worthless in complete obstruction of the pylorus because the dye will not be taken up and the gallbladder may be perfectly normal even though it does not fill.

(4) Is there primary liver disease? If there is primary cirrhosis of the liver or hepatitis, the gallbladder may be normal but the liver may be unable to excrete the dye so that it can be concentrated in the gallbladder and cast a shadow. It is almost worthless to give the dye to patients with obstructive jaundice, because the gallbladder will not fill; this is true whether the jaundice is due to extrahepatic or intrahepatic obstruction. It will fill only in hemolytic jaundice, and usually this diagnosis can be made by other means.

(5) Is the gallbladder in the usual location? That is not quite as silly as it may seem. I recall one patient whose x-ray report was "nonfunctioning gallbladder"—it should have been listed as a nonfilling gallbladder—but by mistake a full-sized abdominal film had been taken and a perfectly normal gallbladder could be seen resting in the right lower quadrant where it hung by a rather long pedicle.

(6) Has the gallbladder been removed? Obviously if the gallbladder has been removed and evidence exists to that effect, it is a waste of time to make a cholecystogram. Conversely, it occasionally may be helpful to order a cholecystogram even though the gallbladder has been thought to be removed. You may find that it has not—we have seen several instances recently where a perfectly normal gallbladder appeared on a cholecystogram despite the fact that there had been a right upper quadrant incision and a cholecystectomy presumably had been performed.

Differential Diagnosis

In connection with acute cholecystitis, one of the most important diseases to rule out is acute disease of the right kidney. Both diseases can cause tenderness in the right upper quadrant; both can produce fever. They usually can be differentiated by means of the urinary findings, but intravenous pyelography or more formal retrograde pyelography may be necessary.

Coronary artery disease may be a troublesome differential point. We recently saw a young woman in her thirties who had been treated for several years for presumptive angina pectoris. Her pain was in the left upper quadrant and substernal. It was not related to exercise, however, and lasted longer than angina. It developed that her real difficulty was gallstones and that she had no organic heart disease whatsoever. In her case the pain was in a rather unusual location.

Acute coronary thrombosis may be a problem in differential diagnosis. In general, the patient with this disease will be much more severely ill, will be in peripheral vascular collapse and will require larger doses of morphine. The electrocardiogram may be of great help in such a situation.

Acute appendicitis occasionally will be quite difficult to distinguish.

Duodenal ulcer with pylorospasm, particularly the milder attack, acute pancreatitis and a whole group of supradiaphragmatic diseases which can be grouped under pleurisy may cause difficulty in diagnosis. Pulmonary infarct certainly may imitate acute cholecystitis, and a pneumonia occasionally may begin in a way which suggests gallbladder trouble.

With the dyspepsias it is extremely important to rule out gastric or duodenal ulcer or even a gastric carcinoma.

Unsatisfactory Results from Cholecystectomy

If we can predict in advance which patient is not going to be happy after cholecystectomy, perhaps we can take measures to avoid such a situation. The largest group of individuals who are dissatisfied with the postoperative results are the neurotic patients in whom the symptoms actually were a result of functional disease. A good many of these patients need the operation, and converting them to satisfied patients largely consists of telling them what they may expect. They should not be told that every gastrointestinal complaint that they have will be cured, that they will feel 20 years younger, and so on. If they have had colic they should be told that it is not likely to recur, but no promises should be made with respect to gas, fullness or intolerance for certain types of food.

The second largest group are patients who have coexistent disease in the stomach, duodenum, liver or pancreas. A patient with gallstones and a duodenal ulcer may be benefited by removal of the gallbladder because it will be easier for him to follow an ulcer regimen, but he should not expect a disappearance of all his gastrointestinal symptoms.

Common duct stones exist in 20 per cent of patients with gallstones. Sometimes these can be diagnosed prior to surgery, but often we must leave it up to the surgeon to find them; unremoved common duct stones will produce symptoms and a dissatisfied patient.

Stricture and cystic duct remnant may cause symptoms and require further surgery.

Biliary dyskinesia is the name given to those residual situations for which no adequate cause can be found. Some patients no doubt have the neuromas which Dr. Womack has described following cholecystectomy and which may mimic gallbladder symptoms.

Common Duct Stone

The usual basis for suspecting a common duct stone is colic—or perhaps I should say pain, plus jaundice. The patient presented earlier actually did not have colic in the strict sense of the word, but a history of jaundice. Colic plus chills and fever means cholangitis. Our patient had one such attack. Here, gallstones plus pancreatitis or a history suggestive of pancreatitis, or recurrent colic after cholecystectomy with or without jaundice, means common duct stone.

My colleagues and I checked the records of a series of patients with common duct stones at the Ohio State University and found that 22 had jaundice, 8 had a history of jaundice, 2 had a questionable history of jaundice, 1 had a history of chills and 1 had had a definite pancreatitis. The significant feature in this series was that 14 of the patients (29 per cent, nearly 1 in 3) had none of the findings usually considered in diagnosing common duct stones.

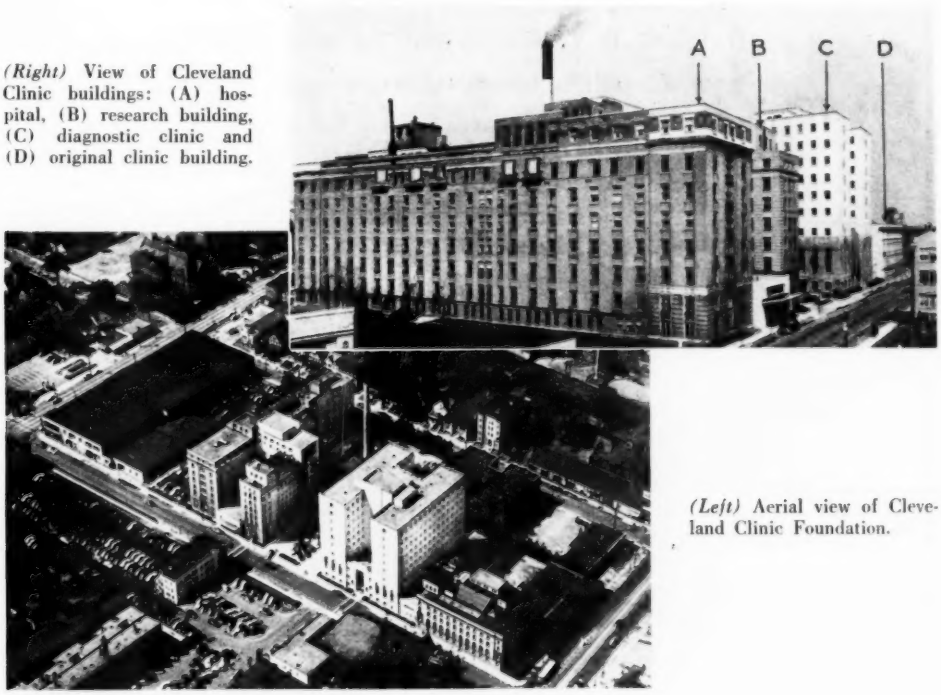
Operative Cholangiography

Operative cholangiography is the most significant tool for the diagnosis of biliary tract diseases that has been added to our armamentarium since development of the Graham-Cole test. It does not require complicated equipment. It does require that the surgeon give up positioning the patient to some extent, because the Bucky frame underneath the operating table interferes with the marked breaks in the table which help in the operation. Also, it requires the closest kind of teamwork between the surgeon, the anesthetist and the x-ray department.

Like any other test, operative cholangiography is not the final answer to problems lying within the bile ducts. It does not replace clinical judgment, nor does it absolve the surgeon from responsibility if he accepts the cholangiogram as apparently normal and a common duct stone is found at a later date.

I had not used cholangiography until about two years ago. Of the first 64 cholangiograms I made, 3 were definitely in error—they were interpreted as being normal and yet common duct stones were present. The explanation for this lies in the fact that small stones may fail to show up even in a good cholangiogram. Even a large stone may be obliterated by an overhang of the common duct. Hence, if a sound clinical indication exists for exploring the common duct, it must be explored. In the first 64 cases the cholangiogram was unsatisfactory in about 1 out of 5 patients. This figure has improved with additional experience, and the technical failures can be almost completely avoided. The cholangiogram was consistent with the clinical findings in about 75 per cent of the cases.

In 2 cases in this series there were no clinical indications for exploring the common duct, and yet these patients had common duct stones. There was no history suggesting a common duct stone, and at operation the common duct appeared normal in size and general appearance and no stones could be palpated. In one of these cases, a plane film showed two radiopaque gallstones of large size. Normally with gallstones of this size, you don't expect to find common duct stones. However, an operative cholangiogram showed two negative shadows which were common duct stones. The patient had not even had very severe colic; she had had no history of jaundice and it was debatable from a symptomatic standpoint whether we should operate on her at all, and yet two common duct stones were discovered by cholangiography.



(Right) View of Cleveland Clinic buildings: (A) hospital, (B) research building, (C) diagnostic clinic and (D) original clinic building.

(Left) Aerial view of Cleveland Clinic Foundation.

Tuberculosis in Children

M. R. Lichtenstein*

and Samson Entin

MUNICIPAL TUBERCULOSIS SANITARIUM OF CHICAGO

Clinical Classification

I. POSITIVE TUBERCULIN—NO LESION ON X-RAY

II. PRIMARY TUBERCULOSIS WITH LESION ON X-RAY

- A. Large Hilus Glands and Insignificant Parenchymal Component
- B. Massive Hilus Glands Causing Atelectasis (So-Called Epituberculosis)
- C. Large Parenchymal Component

III. PROGRESSIVE PRIMARY TUBERCULOSIS

IV. REINFECTION TUBERCULOSIS

Management of Tuberculosis in Children

SEPARATE THE CHILD FROM THE SOURCE CASE

AVOID ANY FURTHER EXPOSURE

TREAT AS A NORMAL CHILD

FOLLOW ROUTINE FOR EACH TYPE (GIVEN ELSEWHERE)

Adapted from an exhibit shown at the Annual Session of the American Medical Association (Atlantic City).

**Chief of Medical Service, Municipal Tuberculosis Sanitarium of Chicago, Illinois.*

FIGURE 1. R. B., 6 year old Negro boy, with positive tuberculin. Normal x-ray. Gastric wash cultures repeatedly negative.

Type I

PRIMARY INFECTION WITHOUT X-RAY EVIDENCE

Diagnosis

SYMPTOMS: Usually none; sometimes a febrile episode resembling mild respiratory infection.

PHYSICAL EXAMINATION: Normal.

X-RAY: Normal.

TUBERCULIN: Changes to positive 3 to 12 weeks following primary infection; usually remains positive for many years.

Management

OBSERVE at intervals (about every six months) with chest x-ray; oftener if any intercurrent disease occurs.

PROGNOSIS: Excellent.

COMPLICATIONS are rare: miliary tuberculosis, meningitis, pleural effusion, bone involvement, etc.

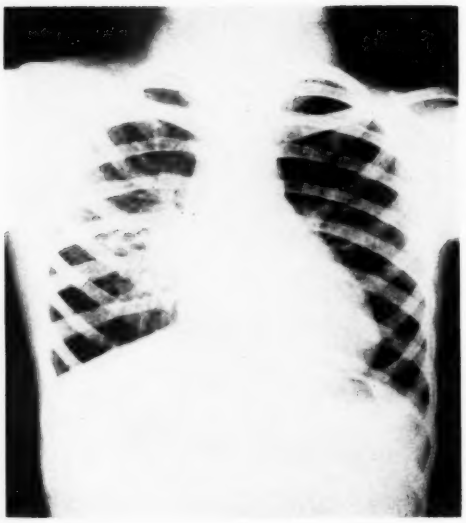


FIGURE 2. C. J., 5 year old Negro girl. Large hilus glands with calcification.

Type II A

PRIMARY INFECTION WITH LARGE HILUS GLANDS ON X-RAY

Diagnosis

SYMPTOMS: Usually none; sometimes mild symptoms and fever.

PHYSICAL EXAMINATION: Usually normal.

X-RAY: Enlargement in one or both hilar regions.

TUBERCULIN: Positive.

LABORATORY: Stomach wash culture positive for tubercle bacilli in 25 per cent of cases.

Course

Glands usually begin to subside in about six months and heal with residual calcification.

Management

IF ASYMPTOMATIC: Treat as a normal child.

Observe and x-ray frequently (about every 60 days for first six months).

IF SYMPTOMATIC: Hospitalize if symptoms do not subside in a few weeks.

Watch closely for complications.

Use antimicrobial therapy if dissemination occurs.

PROGNOSIS: Excellent.

Type II B

PRIMARY INFECTION WITH MASSIVE GLANDS CAUSING ATELECTASIS

Diagnosis

SYMPTOMS: Usually mild; may wheeze.

PHYSICAL EXAMINATION: Signs of atelectasis present.

X-RAY: Evidence of atelectasis, with displacement of trachea, heart and diaphragm toward the lesion.

TUBERCULIN: Positive.

LABORATORY: Stomach wash culture often positive for tubercle bacilli.

Course

Under antimicrobial therapy glands may subside and lung reaerate or atelectatic segment may shrink and become fibrotic, with bronchiectasis.

Management

Hospitalize if possible.

Rest, fresh air, good food.

ANTIMICROBIAL THERAPY: Streptomycin or dihydrostreptomycin daily or twice weekly for three or four months. Supplement with PAS orally if child is able to take it.

Bronchoscopic observation and aspiration of caseous material as indicated.

PROGNOSIS: Generally good.

Cavitation may occur in the atelectatic lung. Dissemination may occur.

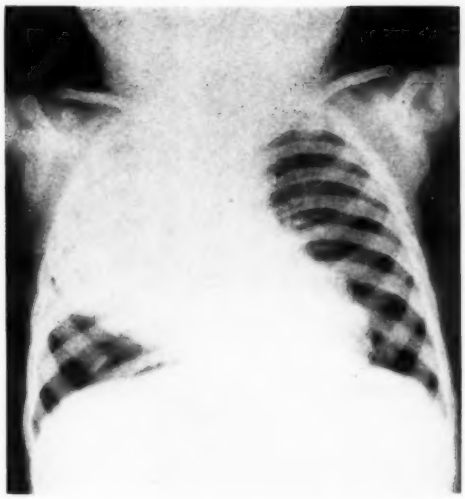


FIGURE 3. L. D., 3 year old Negro boy. Atelectasis of upper lobe of right lung.

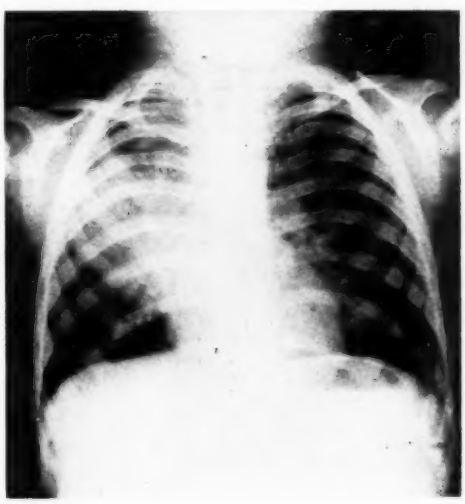


FIGURE 4. L. D., two years later. Marked clearing.

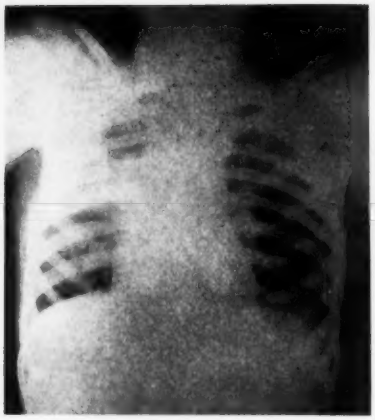


FIGURE 5. H. T. Primary tuberculosis with large parenchymal component.

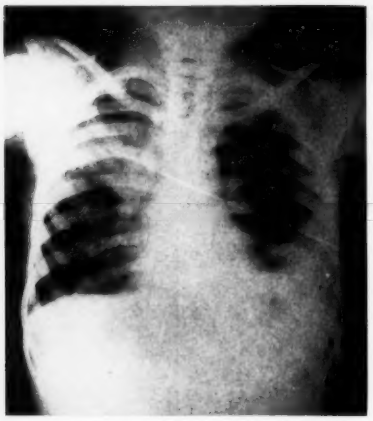


FIGURE 6. H. T. Six months later. Considerable clearing of primary lesion. Pleurisy left base.

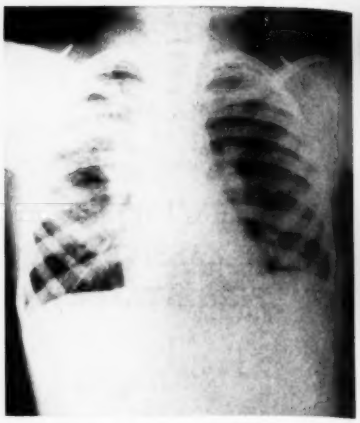


FIGURE 7. H. T. Six months later. Pleurisy improved but progression of pulmonary lesion occurred and child expired.

Type II C

PRIMARY INFECTION WITH LARGE PARENCHYMAL COMPONENT

Diagnosis

SYMPTOMS: Absent to mild as a rule.

PHYSICAL EXAMINATION: Usually insignificant.

X-RAY: Shows parenchymal lesion and hilus involvement on same side.

TUBERCULIN: Positive.

LABORATORY: Stomach wash culture often positive for tubercle bacilli.

Course

Almost always benign. Lesions usually begin to resolve at about six months, but may remain for one or two years. Frequently leave calcifications or fine lines of fibrosis.

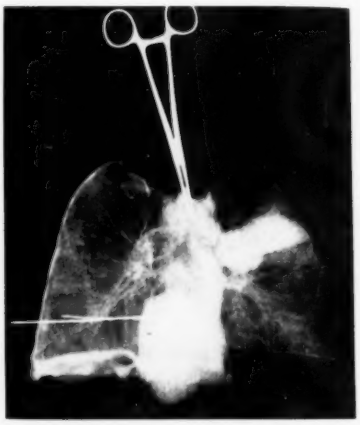


FIGURE 8. H. T. Postmortem appearance of lung demonstrating pulmonary lesion.

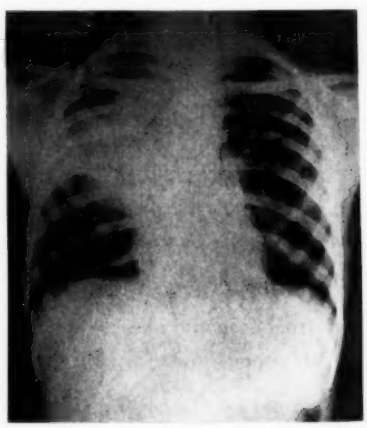
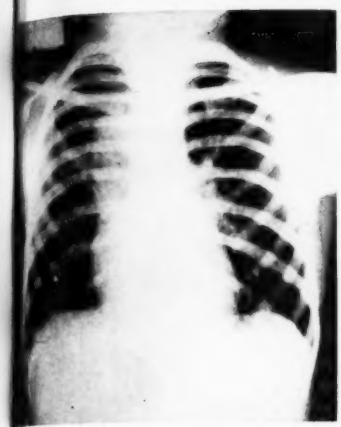


FIGURE 9. J. H., 8 year old Negro girl. Extensive parenchymal involvement of right upper lobe.



URE 10. J. H. Five months later. Considerable clearing.

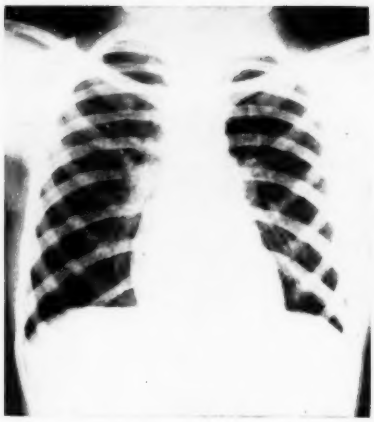


FIGURE 11. J. H. Two years later. Almost complete clearing.

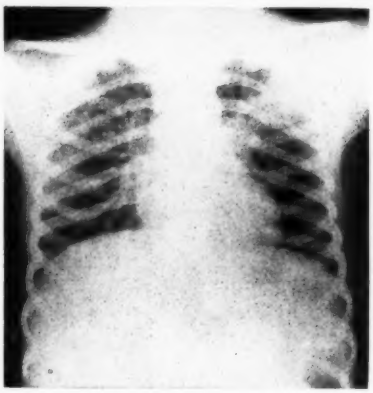


FIGURE 12. C. W., 4 year old Negro girl. Parenchymal involvement of left upper lobe.

Type II C

PRIMARY INFECTION WITH LARGE PARENCHYMAL COMPONENT

Management

IF ASYMPTOMATIC: Leave child at home, and observe with x-ray frequently.

IF SYMPTOMATIC: Hospitalize if possible.

Rest, fresh air, good food.

If symptoms persist beyond a few weeks, or if there are complications, use antimicrobial therapy.

PROGNOSIS: Generally excellent.

COMPLICATIONS: In children under 2 years of age, dissemination, miliary or meningeal involvement may occur with frequent fatalities. This is much more common in Negro and Mexican children.

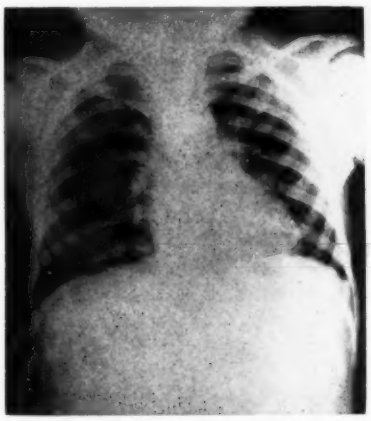


FIGURE 13. C. W. Five months later. Clearing.

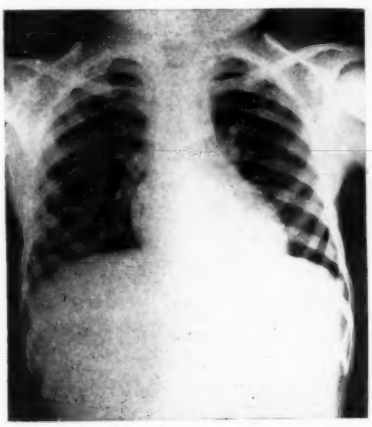


FIGURE 14. C. W. Four months later. Marked clearing.

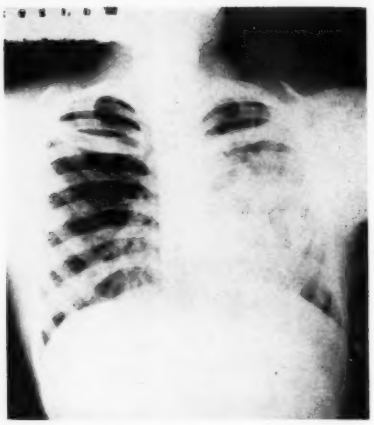


FIGURE 15. A. W., 12 year old Negro boy. Progressive primary involving left lung with persistently positive sputum.

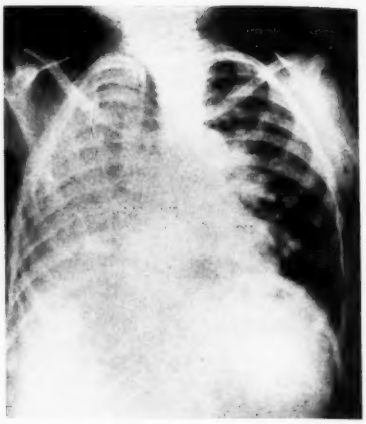


FIGURE 16. C. R. Progressive primary lesion with extensive involvement of right lung and left hilum.

Type III

PROGRESSIVE PRIMARY

Primary fails to resolve, and goes on to destructive tuberculosis, resulting essentially in a picture identical with reinfection tuberculosis.

Diagnosis

SYMPTOMS: May be mild to severe.

PHYSICAL EXAMINATION: Usually reveals abnormal pulmonary findings.

TUBERCULIN TEST: Positive.

X-RAY: Serial films reveal failure of primary lesion to resolve and progression to destructive lesions with cavitation.

LABORATORY: Tubercle bacilli can almost always be demonstrated in the sputum, or gastric lavage culture.

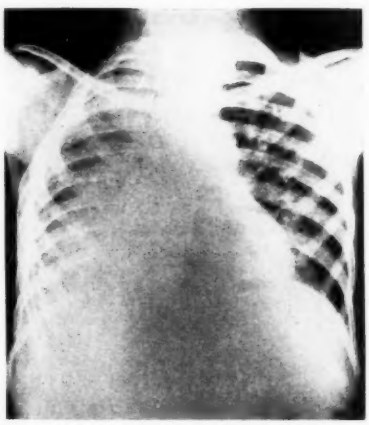


FIGURE 17. C. R. One year later. Marked clearing on streptomycin therapy. Patient asymptomatic.

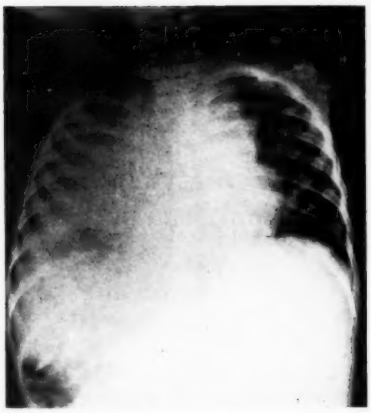


FIGURE 18. H. H., 2 year old Negro girl. Progressive primary. Extensive bilateral involvement.

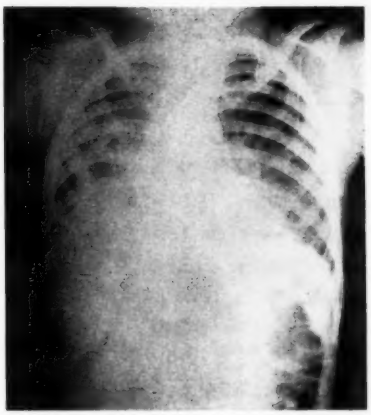


FIGURE 19. C. W., 4 year old Negro girl. Progressive primary. Bilateral involvement. Parents and three siblings died of tuberculosis.

Type III

PROGRESSIVE PRIMARY

Management

REST IN SANATORIUM: Good food; fresh air.

ANTIMICROBIAL THERAPY: Streptomycin or dihydrostreptomycin as indicated.

PAS included for older children able to take it.

COLLAPSE THERAPY: Pneumoperitoneum or pneumothorax can be used in older children.

SURGERY: Thoracoplasty rarely done.

RESECTION: Children tolerate lobectomy very well. Pneumonectomy has a considerable mortality rate.

COMPLICATIONS: Dissemination, with miliary or meningitic involvement, occurs more commonly than among adults, and is frequent cause of death.

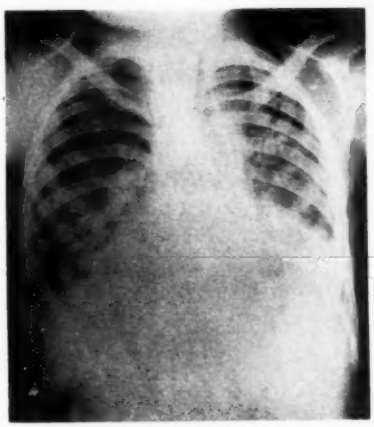


FIGURE 20. C. W. Little change in pulmonary disease but dissemination to abdominal organs occurred. Postmortem examination revealed amyloidosis and ascites.

Type IV

REINFECTION TUBERCULOSIS IN CHILDREN

Destructive disease occurring at a considerable time (months or years) after the primary infection. Identical with phthisis in the adult.

Diagnosis

SYMPTOMS: Mild to severe.

PHYSICAL EXAMINATION: Usually reveals abnormal pulmonary findings.

TUBERCULIN: Positive.

LABORATORY: Tubercle bacilli usually present in sputum or gastric contents.

X-RAY: Reveals destructive pulmonary lesions, usually apical.

Management

HOSPITALIZE: Rest, fresh air, good food.

ANTIMICROBIAL THERAPY: Streptomycin or dihydrostreptomycin; combine with PAS if possible.

COLLAPSE THERAPY: Pneumothorax or pneumoperitoneum can be used in larger children. Thoracoplasty and resection are rarely used.

COMPLICATIONS: Dissemination (miliary, meningitic, etc.) is common in children, especially nonwhites. Mucous membrane involvement (bowel, bronchi, larynx) is frequent.

PROGNOSIS: Generally poor unless adequate collapse is obtained. Very poor in the presence of dissemination.

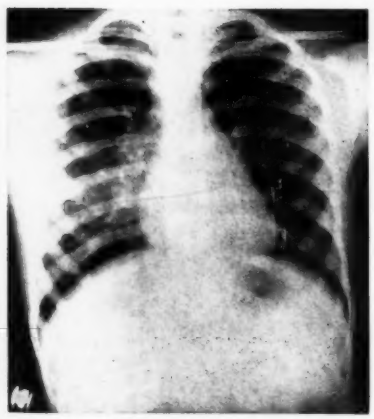


FIGURE 21. F. F., 6 year old Mexican girl. Healed primary tuberculosis. Remained well for five years after this film was made.

FIGURE 22. F. F. Six years later. Reinfection. Extensive bilateral disease. Positive sputum.

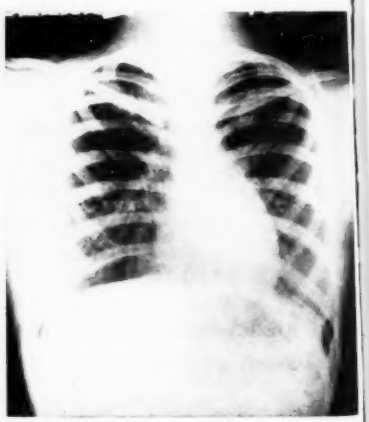


FIGURE 23. F. F. Seven months later. Marked clearing on streptomycin therapy.

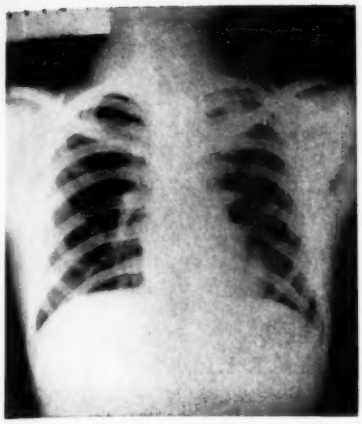


FIGURE 24. R. J., 11 year old white boy. Reinfection tuberculosis of left lung.

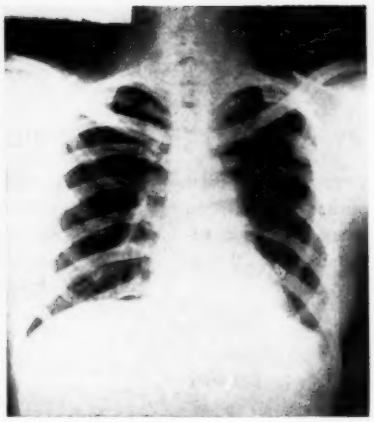


FIGURE 25. R. J. Four months later. Marked clearing under streptomycin therapy. Sputum still positive.

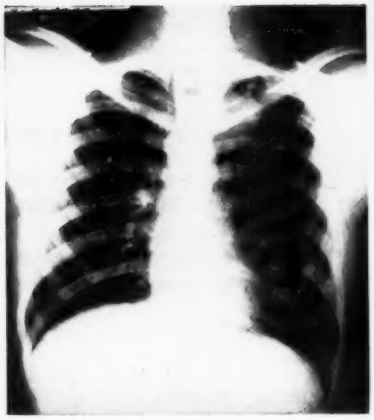


FIGURE 26. R. J. Left pneumothorax. Sputum now negative. Note apical adhesion.

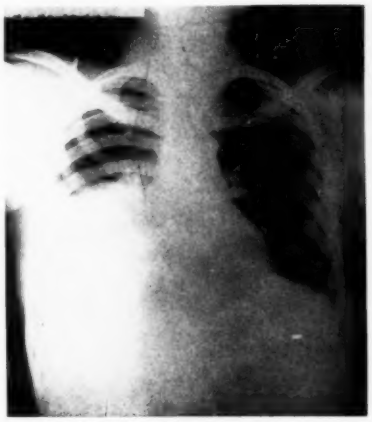


FIGURE 27. D. J., 1 year old Negro boy. Extensive involvement of right lower lobe.

FIGURE 28. D. J. Lateral view showing involvement of right lower lobe.

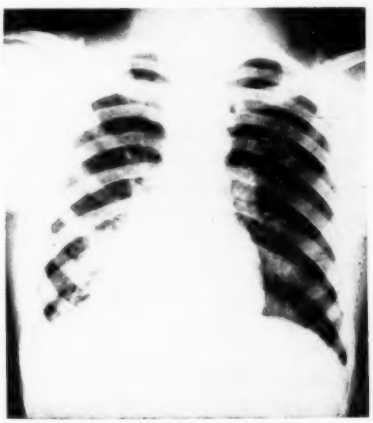


FIGURE 29. D. J. One year later. Considerable clearing but sputum remains persistently positive.

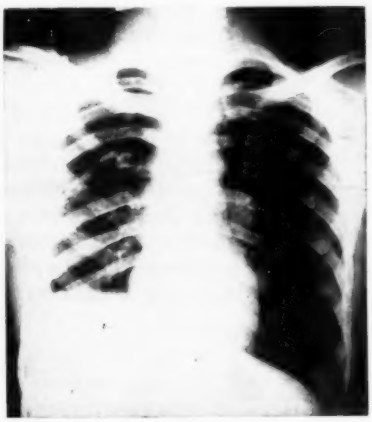


FIGURE 30. D. J. One year later. Lobectomy performed. Asymptomatic. Sputum negative. Patient discharged.

ANTIMICROBIAL THERAPY

STREPTOMYCIN OR DIHYDROSTREPTOMYCIN: Given intramuscularly, in one dose; either daily, twice per week, or three times per week. Children require relatively higher doses than adults. 20 mg. per kilogram or more may be given.

SUGGESTED SCHEDULE:

Wt. of child in pounds	*Grams per day*
Less than 10	0.3
10 to 19	0.4
20 to 39	0.5
40 to 59	0.6
60 to 89	0.75
90 and over	1.00

Continue for 90 days, or longer if indicated.

Sodium para-aminosalicylate should be given daily, 8 to 16 gm., divided in 3 or 4 doses, after meals. Preparation: 20 per cent solution in water, flavored.

TUBERCULIN TESTS

MANTOUX METHOD: Inject 0.10 cc. of solution intracutaneously so that it raises a definite wheal; place on forearm, arm or back; read in 48 hours or 72 hours by palpation; test is positive if induration over 0.5 cm. in diameter is felt.

MATERIALS: Start with O.T. 1:10,000 or P.P.D. first strength; if negative continue with more concentrated solutions (P.P.D. second strength, or O.T. 1:1000, etc.).

All children with tuberculosis will react positively unless moribund; those with miliary or meningeal tuberculosis may require strong concentration. Nonreactors should be considered nontuberculous unless proved otherwise.

CRITERIA FOR SANATORIUM CARE OF CHILDREN WITH TUBERCULOSIS

A. The following types of cases definitely require sanatorium care:

1. Miliary tuberculosis.
2. Tuberculous meningitis.
3. The adult type (destructive type) of tuberculosis. X-rays should usually reveal evidence of cavitation. Tubercle bacilli should be demonstrated by positive sputum, stomach wash culture, bronchoscopic aspirate culture or guinea pig inoculation.
4. Progressive primary tuberculosis with tubercle bacilli demonstrated as above. In order to be classified as a progressive primary lesion there should be x-ray evidence of parenchymal inflammatory disease, which has failed to resolve after several months of observation.
5. Primary tuberculosis type IIB (massive hilus glands with atelectasis).

B. The following types of cases do *not* require sanatorium care:

1. Primary tuberculosis as indicated by a positive Mantoux test with evidence of enlarged glands in the mediastinum or elsewhere, but without parenchymal disease.
2. Primary tuberculosis as evidenced by a positive Mantoux test, plus a parenchymal pulmonary lesion of less than four months' duration.

C. Exceptional cases: Patients who do not fall definitely within one of the above classifications may be considered on their individual merits.

Pediatrics IN GENERAL PRACTICE

For general practitioners, who handle more than 85 per cent of all pediatric care, POSTGRADUATE MEDICINE *here presents authoritative, up-to-date summaries, prepared by specialists in pediatric problems.*

Primary Atypical Pneumonia in Children

ALTON GOLDBLOOM*

McGill University, Montreal, Canada

A. GOLDBLOOM

THE term "primary atypical pneumonia" has led unwittingly to a maze of semantic confusion. The term arose insidiously, not because a new entity had been discovered, isolated and accurately described but rather because with the beginning of the sulfonamide era it was applied to that residue of cases of pneumonia that did not respond to the new drugs in the same manner as did most, but not all, cases of pneumococcal pneumonia. Pneumococcal pneumonias which run a "typical" course are seen rarely nowadays, and few students or young interns have ever seen a case in which the fever was permitted to fall by crisis on the ninth day—even when the patient was admitted to the hospital on the evening of the eighth day of disease. Typical pneumonia is no longer typical—what, then, is atypical pneumonia?

We cannot say that typical pneumonia is caused by bacteria and atypical pneumonia by a virus. Many bacterial pneumonias in children with lobar or lobular distribution and showing elevated neutrophil counts in the blood will nevertheless run a course uninfluenced by antibiotics and with a lytic course of temperature. These properly could be called atypical pneumonias. Now comes the confusing word "primary" which at once begs a very big question. Is any pneumonia truly primary? Do we ever speak of primary meningococcus meningitis? I believe that the term "primary atypical pneumonia" takes for granted knowledge which we do not yet possess.

The diagnosis is essentially one of exclusion. It is what remains after we have ruled out those pneumonias which are lobar or lobular in distribution and other pneumonias caused by culturable bacterial agents. What is left is an ever growing group of pneumonias, some caused by or associated with viruses, and many assumed but not proved to be of viral origin. To this vague and heterogeneous group, the term primary atypical pneumonia is being indiscriminately and often erroneously applied. There is no single pneumonia which by clinical or laboratory tests can be

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shown to belong to one specific category and to which the term can be applied unequivocally in the manner, for instance, that we are able to say that a certain pneumonia is caused by a certain pneumococcus.

The search for a single etiologic agent so far has been fruitless. Horsfall wrote as follows: "Despite many attempts to recover the infectious agent or agents, there is not yet complete agreement among investigators as to the nature and identity of the causal agent—despite very thorough investigations by a number of competent workers."[1]

Many types of pneumonia seen in children are apparently not caused by bacterial agents. These pneumonias run varying courses during which the temperature is not greatly elevated and the physical signs are elicited more readily than is roentgenologic corroboration and vice versa.

Just as there are no physical signs by which the condition can be recognized, so there are no roentgenologic signs that will differentiate a condition to which we can unqualifiedly assign the term primary atypical pneumonia. The roentgenologist cannot differentiate with certainty those pneumonias due to aspiration of oil from those caused by viruses or from those associated with mucoviscidosis. Nor can he more than suspect from the lobar or lobular distribution of densities that a given pneumonia is of bacterial etiology. Whatever has been written about the roentgenologic findings in this disease can apply equally well to many other forms of pneumonitis—bacterial, viral or from other causes.

If we attempt to rely on laboratory tests to corroborate our diagnosis of primary atypical pneumonia, we again find that there is no single test or group of tests which invariably determines the diagnosis for us. In most of these cases the leukocyte count is not elevated; often it is reduced and the neutrophils are diminished in number. It is incorrect to say that there is a lymphocytosis, for the lymphocytes may be either normal in number or even somewhat diminished. Even the term relative lymphocytosis should not be used, for it sets into motion mental processes which lead to the erroneous assumption of absolute increase. While cold agglutinins have been found in 30 to 50 per cent of cases, and agglutinins to certain nonhemolytic streptococci in others (MG strain, etc.), there is no real correlation between the two or between these and any other laboratory tests.[2,3]

There are pneumonias in children—as in adults—apparently of viral origin, that are not caused by a single virus but rather by a variety of infective agents that produce similar clinical pictures. Only a few of these pneumonias are subject to differentiation, even by extensive laboratory investigations. Among the agents known to cause such pneumonias are the influenza virus, the basophilic viruses of psittacosis (ornithosis), the pneumonitis group, lymphocytic choriomeningitis, *Rickettsia burneti* and infectious mononucleosis. Recently Adams[4] has suggested that the virus of canine distemper may also cause a pneumonitis in children, similar to the melange into which primary atypical pneumonia has been inextricably mixed. In addition tularemia, coccidioidomycosis and some forms of tuberculosis may present clinical manifestations indistinguishable either from bacterial pneumonias or from what is called primary atypical pneumonia.

Many pneumonias in children tend to run an atypical course. There may be slight fever and abundant physical signs; there may be high fever and few or no physical signs but a surprising amount of infiltration evidenced only by roentgenologic examination. Bacterial pneumonias may run a long, indolent course and nonbacterial pneumonias may run a short course which makes clinical differentiation extremely difficult. Constitutional signs may be extremely variable and the whole picture may be masked by severe gastrointestinal manifestations which often require urgent treatment to prevent death, not from pneumonia but from the ensuing dehydration and electrolyte loss. Only the rapid response to antibiotic treatment will help to differentiate between one group of pneumonias and another, aided, of course, by the bacteriologist's report. There is no real unanimity of opinion as to the value of the antibiotics in those pneumonias not of known bacterial origin.

Nor do children invariably respond to bacterial pneumonias with a brisk increase of the total leukocytes and neutrophils. Indeed, many do, but we have no right to assume that those who do not are suffering from nonbacterial pneumonias, except perhaps where there is a leukopenia.

Coming back now to our semantic maze—we have invented a term "primary atypical pneumonia" and we are confusing the name with the disease. Because we have coined the phrase, we assume that such a condition exists and we are uncritically assigning the term to a disease whose nature and etiology are as yet undefined. The diagnosis is still one of terminology, not of fact. We have not the slightest proof that it is primary. The designation "atypical" is grossly misleading. Every case of pneumonia, from whatever cause, is different from any other case of pneumonia that has ever existed; therefore all pneumonias may be said to be typical in being atypical. The term has no etiologic connotation whatever and contributes greatly to dulling our thinking processes by suggesting that because the term exists, it therefore represents a specific thing.

That there are bacterial pneumonias we well know, and we have also recognized for some time that many other agents—nonbacterial and nonviral—may cause pneumonias in children. Lipid pneumonia is one example, *Ascaris* larvae is another, and so too are chemical irritants. It was the advent of the new era of antibiotic therapy that quickly brushed away those pneumonias, readily, dramatically cured by these agents, and has left us with a residue of pneumonias not amenable to such treatment. Research in the field of viruses and rickettsial diseases and a far greater number of roentgenologic examinations of children's chests have given us a perhaps erroneous impression of an increase in pneumonitis due to nonbacterial agents.

It is far better not to use the term primary atypical pneumonia. It is better to refer to bacterial and nonbacterial pneumonias and, until better diagnostic criteria are available, to assume a viral etiology by exclusion or by whatever corroborative evidence may be available. This will at least remove the feeling of finality from our minds and leave us receptive to the real solutions whenever and however they may be found. Accepting *the term* as *the disease* carries with it the danger of not searching for the foreign body, not examining the stools for *Ascaris ovis*, not searching for tubercle bacilli in the sputum, indeed not making the host of investigations which will help us to differentiate one form of pneumonia from another. What is particularly fascinating about pediatrics is that children tend to have typical diseases in an atypical manner and pneumonia is no exception.

REFERENCES

1. Rivers, T. M.: Viral and Rickettsial Infections of Man. Philadelphia, J. B. Lippincott Company, 1948, p. 290.
2. Van Rooyen, C. E. and Rhodes, A. J.: Virus Diseases of Man. New York, Thomas Nelson & Sons, 1948.
3. Reimann, H. A.: Viral pneumonias and pneumonias of probable viral origin. Medicine 26:177 (May) 1947.
4. Adams, J. M.: Primary pneumonitis in infancy. J.A.M.A. 138:1142 (December) 1948.

POSTGRADUATE COURSES

University of Minnesota Medical School, Minneapolis: Continuation course in medical economics for physicians, October 30-31.

Continuation course in fractures and the surgery of trauma, November 13-15, intended for general practitioners.

Continuation course in endocrinology, December 4-6. Intended primarily for general practitioners. Guest faculty member will be Dr. Dwight J. Ingle; director is Dr. C. J. Watson.

Boston University School of Medicine and Massachusetts Memorial Hospitals: Course of clinical lectures and demonstrations for practicing physicians. Wednesdays from 2:00 to 4:00 P.M., October 22, 1952, to April 29, 1953, in the Evans Memorial amphitheater at Massachusetts Memorial Hospitals. Course will be directed by Dr. Chester S. Keefer and will include 50 hours of instruction. For further information, write Dr. James M. Faulkner, Boston University School of Medicine, 80 East Concord Street, Boston 18, Massachusetts.

GENERAL PRACTICE *Review*

This department offers the latest, proved methods for the treatment and management of commonly encountered conditions based on the extensive experience of the physicians who prepare these summaries for POSTGRADUATE MEDICINE.

Senile Cataract: A Geriatric Problem

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WHEN one of my colleagues, who is not an ophthalmologist, was asked what he would like to know about senile cataract, he replied that he would like an explanation of exactly what a cataract is, what the symptoms are, what the fate of it may be if not operated on, why it has to be ripe and the time of life when it occurs. He said that he would not be interested in the details of operative technic. With this information as a guide, I shall discuss some of the points which may interest physicians who are not ophthalmologists.

What is a Cataract?

A cataract is an opacity in the crystalline lens. The name (from the Greek—to rush down) comes from a misconception of both the anatomy and pathology, and apparently originated at the time of Galen in the second century A.D. Galen stated that *hypochyma*, as the Greeks called it, was formed by a falling down of coagulated fluid behind the iris. He thought there existed behind the iris a large space, which he termed the *locus vacuus*, where a coagulated humor fell down and obstructed the pupil.

There are many different types of cataracts with differing etiologies, such as the diabetic, congenital and traumatic, to name only a few of the nearly 50 mentioned by Duke-Elder, but we are concerned here only with the senile type. The etiology of the so-called senile cataract is unknown but it is believed to be due to a nutritional disturbance of the lens. The incidence of senile cataract is greatest among persons over 70 years of age, although cataracts indistinguishable from those seen in elderly people occur in persons as young as 20 years old and in all intervening decades.

The crystalline lens, like other tissues of the body, carries on certain metabolic processes. It receives nutrient chemicals and discharges chemical waste. It is not supplied by blood flow for the obvious reason that opaque

blood would interfere with vision. It receives its nutrition through the aqueous humor, which is produced by the ciliary body by a combination of filtration of the blood and by active secretion. The ciliary body is, in a sense, the heart of the eye. It produces the aqueous, sends it into the interior of the eye and maintains a pressure which causes it to circulate and eventually to flow out through the filtration angle, where it returns to the blood stream. The passage of the fluid and dissolved chemicals into the substance of the lens presumably occurs by osmosis through the capsule of the lens. It is conjectured that changes—which may be rather minor—in the chemical reactions that take place may denature the transparent proteins of the lens, causing it to lose its transparency, somewhat like the change which occurs in the white of an egg when it is heated.

In general, there are three areas in the lens which may be primarily affected: (1) The embryonic nucleus, which lies in the center, may become clouded. (2) Changes may occur in the cortex, near the capsule, which produce radiating opacities in the peripheral part of the lens. These may be in the form of bars or may be club-shaped, tear-shaped, needle-shaped or may appear almost like feathers, as the lamellas separate from one another. (3) Another point of predilection is just at the posterior pole of the lens, near the capsule, where degenerative changes occur with the formation of crystal-like opacities, which sometimes reflect all the colors of the rainbow when a light is thrown into them.

One never knows, when examining a cataractous lens, how many years previously these changes began. If one passes a beam of light obliquely through the normal lens at any age, even in childhood, the beam looks a little smoky. The crystalline lens is never optically empty, as is the aqueous-filled anterior chamber which lies in front of it. There is no definite demarcation between this physiologic haziness and the haziness of early cataract. Cataract formation begins many years before the patient is aware of it and many years before there is interference with vision.

The history which the patient presents is exceedingly simple: He no longer sees clearly. Typically, he places the time of onset two or three years earlier, although the ophthalmologist may have a description in the patient's record of cataractous changes some 10 to 15 years previously. The patient may sometimes amplify the statement that his vision is not clear by saying that it seems as though the room were full of smoke or that everything looks cloudy or that there are many spots before his eyes whenever he looks at sky, water, snow or a light-colored, plain wall.

Arriving at a diagnosis is usually as simple and easy as eliciting the history, unless the cornea is so cloudy that the crystalline lens cannot be examined. Much more difficult, and of equal importance, is the diagnosis of other ocular pathology. It is of no use to remove the cataract from an eye in which the retina has been destroyed by glaucoma or arteriosclerosis or in which the macula is covered by hemorrhages and exudates from diabetic retinitis, arterial hypertension or Kimmelsteil-Wilson syndrome, or in which there is detachment of the retina or a host of other blinding diseases. Arteriosclerosis is especially common and can result in very extensive, destructive changes in the retina. Sometimes it taxes all of the diagnostic acumen an ophthalmologist possesses to determine whether the blurring of vision is due to opacities of the lens or to something else. When the lens is so cloudy that the retina is invisible it may become impossible to diagnose rather extensive retinal disease, but every effort should be made to do so.

The steps which should precede advising cataract operation include examination of the adnexa for infection, measurement of the tension of the eye to exclude glaucoma, dilation of the pupil for examination of the cornea, iris and lens by means of a microscope and careful fundus examination and, surprisingly enough, a painstaking refraction. Occasionally a patient exhibits a lens so cataractous that it can be spotted across the room; his vision is down to less than the biggest letter on the chart, but when he is refracted, he is found to have reasonably good vision. As long as the patient sees fairly well for distance, reads

without very much difficulty and is satisfied with his vision, one is not justified in intervening surgically.

A general physical examination is of paramount importance and the person most suited to carry this out is the patient's family physician, especially if he has known the patient for some time. The average senile cataract patient is not a good surgical risk but may be operated on for cataract safely, because the physical shock from this particular operation is trifling and the local anesthetic usually is not very disturbing. It is important that the ophthalmologist know of the existence of heart disease, cardiorenal disease, diabetes or blood dyscrasias and he should be particularly interested in having an adequate idea of the patient's personality. Heart disease itself is not a contraindication to cataract extraction unless the patient is actually decompensated; in fact, the 10 day convalescent period may give the heart some much needed rest.

The Treatment of Cataract

Celsus (A.D. 30), who believed that a cataract was "a suffusion . . . which sometimes obstructs the pupil of the eye," stated that if the cataract were recent, one could sometimes, by the use of certain measures, succeed in dissolving it . . . but, if it were old, it required an operation by hand which might be among the most delicate in surgery. The best ophthalmologists ever since Celsus have agreed fully with this therapy, except that the secret for dissolving the early cataracts must have died with Celsus; no one, since his time, has ever been able to find anything that dissolves them. As far as we know now, there is only one treatment which has any influence upon a cataractous lens (senile) and that is surgical removal. We still sometimes use DIONIN®, a derivative of morphine, in the hope that it will delay further progress of cataract formation, but whether it ever actually accomplishes this purpose is difficult to say.

The surgical treatment of senile cataract is an old procedure, its history extending back into antiquity for at least 3000 years. Until modern times the operation invariably consisted of "couching," i.e., trying to detach the cataract from the zonular fibers by which it is suspended and depressing it out of the line of vision behind the iris.

Couching was still done in India when I was doing eye surgery there in 1934 and the results were very poor. The modern technic consists, of course, in complete removal of the lens—but more of that later.

Twenty years ago it was the custom to wait until a cataract was ripe or mature before extracting it. This meant that opacification had been carried to a high degree and that the cortex had degenerated so that it could readily be loosened from the capsule. At that time, we were taught to open the capsule of the lens and express the contents. If the cortex was sufficiently degenerated, the capsule could be emptied easily and effectively. The capsule was left in place and in 15 or 20 per cent of the cases either was already more or less opaque or became so. This was called "after-cataract" or secondary cataract and necessitated having a hole cut through it by a subsequent operation called discission. Invariably, with the capsulotomy, there was some cortex left in the eye and about 10 per cent of all eyes operated on developed more or less iritis due to the irritation of this lens protein. Iritis, which sometimes was so severe as to destroy the eye, used to be one of the most feared and serious complications. Now, we remove the lens within its capsule and, from the standpoint of surgical consideration, it is no longer important that the cataract be mature. Patients need no longer go through several years of semiblindness waiting for the proper time to operate, and we have practically dispensed with secondary operations and have largely avoided the complicating iritis.

What happens to the cataract if nothing is done? It simply becomes absolutely opaque and white and eventually shrinks and becomes hard; it may become calcified. Of course, the patient remains blind.

Geriatric Considerations

After senile cataract is diagnosed and the decision made to operate, much remains to

be considered, especially from the standpoint of geriatrics. These patients are elderly and, as far as possible, one must determine their degree of senility. The surgeon must estimate the patient's morale and his general outlook on life, a task which is sometimes difficult because some of these patients are silent, diffident, uncertain, unhappy and volunteer no information. The status of the family relationships must be evaluated.

If a patient is so senile that he shows much mental deterioration, with rare exceptions, he should not be operated on. If his morale is poor, the etiologic factors should be sought and their elimination, if possible, effected. Although there is only minor physical shock, it must be recognized that there is considerable mental shock in a great many of these patients; this results in a slow convalescence and even in psychosis, if improperly estimated and managed.

Although there should be no physical shock, some patients, even though emotionally well integrated, may be left in a weakened physical state for months and they may be left with a horror of the operation. Two instances come to my mind in this category; in both cases the vision obtained was good and in neither was there any pain or other complication, yet both patients were feeble for several months and would not even talk about an operation on the second eye.

Cataract patients in general are in physical decline and, either consciously or unconsciously, sense it strongly. Some of them feel uncertain and indecisive, small things loom large and they may have many deep, secret fears. By no means are all senile cataract patients in this state of mind; many are perfectly calm and surprisingly self reliant. One must seek in many ways to uncover fears and uncertainties.

Among the apprehensions which one may discover in this group of patients are these:

The fear of becoming a burden to the family. They are already dependent, do not like it and are not sure that the love and affection of those about them are sufficient to carry an added load. Some fear that one or more members of the family are unwilling to assume the burden of an operation.

Some patients worry about the financial burden. On this score, they may be reassured by being told that doctors have a sliding scale in caring for people in their age group and that a charge commensurate with their ability to pay can be settled beforehand. They should be impressed with the fact that physicians at large never deny services for financial reasons and if a person is without means, the operation will be done for nothing. To know that this is the universal attitude of physicians seems to give them assurance.

Many of these elderly patients fear pain but will say nothing about it. It is, therefore, wise to bring up the subject and inform them that there will be no pain associated with this surgical procedure.

Some of them are afraid of a general anesthetic and are comforted to know they need not be put to sleep for the operation.

Others feel that they are too old to tolerate surgery; it helps them to know that the majority of cataract patients are in their age group and get along very well.

Almost universally these patients fear blindness and they seek to hold what vision they have. They should be informed that the prognosis is good and every means should be employed to allay this apprehension. They receive reassurance by talking with some other patient who has recently had the operation and has experienced the return of vision. Cataracts rarely develop evenly in both eyes and, therefore, the matter of selection of the eye to be operated on presents itself. Some prominent ophthalmologists feel it is easier for the patient postoperatively if the better eye has been selected and it is their habit to operate on the better eye first. However, it seems to me that it relieves this apprehension of becoming blind to allow the patient to select the eye himself. With few exceptions, he will select the poorer eye.

To some, the hospital is an unfamiliar and awesome institution, even though in the past 25 years there has been a rather favorable change in this attitude. A certain number express doubt that they can remain in bed for so long a period, while still others have heard

that they must lie flat on their backs in bed without moving a muscle and this they feel unable to do. This used to prevail in the management of cataract patients but we have now developed technics which make it possible for the patient to be out of bed almost immediately and this reassuring explanation is given the patient ahead of time.

Some of these people are chronically constipated and habitually take something for this difficulty. It helps them to know that they may take the medicine they have at home and use it at the hospital.

In a word, it is important in the management of the elderly cataract patient to probe for fears and to seek to answer unasked questions. Kindness, friendliness, assurance, tact and optimism rank equally with manual dexterity and medication. Experience has shown that it is often wise to make harmless compromises in management, or even sometimes compromises which are not so harmless as far as the eye is concerned, if it is better for the patient as a whole.

During the operation itself it is wise to avoid demanding too much cooperation lest the patient become worried for fear he is not doing well. If directions are given to him at all, they should be in positive rather than negative terms. Instead of requesting him not to turn his eye up, it is better to ask him to look down as though he were walking, and it seems to me that patients get along better if no directions at all are given and if silence is maintained in the operating room, as far as possible. Under ideal conditions, including silence, many patients will doze during the operation.

Happiness and contentment during the postoperative period are imperative for an uneventful convalescence. One must be alert for disorientation and postoperative psychosis, which sometimes occur during the one or two days when both eyes are bandaged. These complications are treated by opening at least one eye promptly and urging the patient to sit up in bed or in a chair so that he may orient himself. Prevention of these disturbances lies in a proper evaluation of the patient's mental attitude before operation and in allaying as many of his fears as possible. The postoperative patient whose eyes are both covered should never be left alone and, for this reason, it is wise to have him in a room with another patient to whom he can talk and/or to have some member of the family present most of the time.

In order that these elderly patients do not lie in one position too long or remain overlong in bed, on the day of operation they are turned from side to side frequently by the nurses and on the first postoperative day they are permitted to sit up in bed. Routinely, on the second postoperative day, one eye is uncovered and the patients are allowed to sit up in a chair. In order to keep the circulation of the lower extremities active, patients are instructed to wiggle their toes frequently and massage is sometimes given. I have seen 2 cases of pulmonary embolism complicating a cataract extraction, 1 of which terminated fatally. An attempt to obviate pulmonary stasis is made by frequent turning and early ambulation and, if necessary, a little carbon dioxide is employed. Constipation must be combated. With the operative technic in vogue 20 years ago such freedom was not possible. The patient used to be immobilized flat on his back for a week, with sandbags on each side of his head, and was actually forbidden to have a bowel movement. That was thought to be necessary because the margins of the incision were not closed by sutures but merely lay in apposition and had to heal before motion could be allowed. If the present technics are properly applied, the incision is firmly and tightly closed by strong sutures directly in the wall of the eye. Frequently the aqueous chamber is already half re-formed by the time the dressing is applied.

Modern technics have eliminated a number of most dreaded complications that used to occur. Iritis is now rare and it formerly was common. Herniation or prolapse of the iris was frequent. It rarely occurs now. Postoperative bleeding into the anterior chamber still occurs sometimes, but this also can be eliminated by proper technic. Postoperative glaucoma is not common but still occurs and is very difficult to manage. True postoperative

glaucoma does not respond to the usual medical or surgical management of glaucoma. The difficulty is often a mechanical one and is due to the fact that aqueous may leak from the anterior chamber for some days, thus causing the iris to lie flat against the cornea and over the filtration angle. When the leak at last closes, the iris may fail to float free and continues to obstruct the outlet at the filtration angle, which may result in a distressing increase in intraocular pressure.

By and large, most patients get along very well and at the end of six weeks are fitted with lenses, with which they may, and frequently do, have 20/20 vision.

This would seem to be the end of the surgical adventure, but such is not always the case. A blind patient has come to us; we have successfully removed a diseased part of his visual apparatus, replaced it with an artificial glass lens with which he sees well, but he is dizzy and objects close at hand are not located where they appear to be. He goes home happily and at the dinner table attempts to put a spoonful of sugar into his coffee. He sees the cup clearly, he sees the spoon clearly, he tips the sugar out and it falls on the near side of the cup, even missing the saucer. The patient, using his new lenses, starts upstairs for bed, reaches for the balustrade and cannot find it; he tries to put his foot on the bottom step and the step isn't there.

The explanation for this phenomenon lies in the fact that the eye itself actually does not see. It sends signals into the visual cortex in the occipital lobe where they are constructed into an image. It is thought that vision does not occur here either, because when the visual cortex is stimulated during a brain operation, form does not result—only light. True vision does not occur until the stimulus enters consciousness, and no one knows just where this is located or if it has a definite location in the brain. One might say that the eye is a television camera, the visual cortex a television screen (oddly, it is absolutely dark in there) and the observer is consciousness. Our figure of speech involving television breaks down when we speak of the image on the screen; as a matter of fact, only certain signals come into this screen which are observed by consciousness and from which consciousness improvises an image.*

In removing the crystalline lens in cataract surgery and replacing it with a glass lens in front of the eye, we have altered the lens system and the size of the image which falls upon the retina. When the signals thus elicited are transmitted to the brain and to consciousness, they are misinterpreted, especially as to localization. The conscious mind must relearn a skill and interpret the retinal stimuli on a new basis. In most patients this adjustment takes place rather rapidly. They are enthusiastic over the keenness of their new vision and apply themselves assiduously to acquiring the necessary skill in its use.

The patient must pass through a period of rehabilitation, a time of trial and error, which is sometimes discouraging and often very confusing. This is more especially so if the eye he is trying to learn to use is the nondominant one and/or it has been blind for many years. These difficulties must all be explained to the patient before his operation so that he knows what is coming and is prepared to meet it.

On the whole, the visual results of cataract surgery are good. Of all patients operated on, including those having diabetic and hypertensive retinitis, about 3 out of 4 attain normal visual acuity. If all eyes with conditions other than cataract are excluded, i.e., a selected series which has nothing pathologic excepting cataract, about 9 out of 10 attain normal visual acuity. We have a right to feel proud of such results—might we add after 3000 years of trying! We are fully justified in presenting to the prospective cataract patient a hopeful and cheery outlook for useful vision.

*The fact that the brain improvises vision can be illustrated by the following simple experiment: If the forefinger of one hand is held vertically 12 inches in front of the face and the eyes fixed on a doorknob across the room, the finger will appear to be double and will seem to be normal in color and opaque, as fingers should be. If the hand now is moved to one side or the other in such a manner that one of the double images covers the doorknob, it will be seen that the finger becomes transparent in that portion which covers the doorknob, and the knob will be seen through it.

Editorials

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NONARTICULAR FORMS OF RHEUMATIC DISEASE

MUCH is being written these days concerning the classic forms of arthritis, especially rheumatoid arthritis, rheumatic fever and gout. Not nearly enough is being said about the various nonarticular forms of rheumatic disease, which are really much more prevalent than the abovementioned articular forms. Nonarticular rheumatism attacks various structures in the locomotor system, particularly tendons, muscles, nerves and connective tissue. These nonarticular forms either may occur in association with frank arthritis or may be entirely independent of any joint lesions.

Patients with rheumatoid arthritis frequently complain of pain not only in the affected joint itself but also in adjacent parts. In arthritis of the knee, pain may also exist in the calves; in arthritis of the hip, there may be pain in the groin or the inner side of the thigh; in arthritis of the neck and shoulder, pain also may be noted in the forearm or fingers. Much of this is referred pain. However, one cannot but feel that at least some of this pain in the soft tissue is due to actual infiltration of inflammatory cells into the muscles and connective tissues. This suspicion is supported by the studies of Freund and his co-workers[1] who first described the presence of inflammatory cells in the muscles and nerves of patients who have rheumatoid arthritis.

In rheumatic fever the so-called "growing pains" are not limited to the joints proper but often make their appearance in the muscles of the arms and legs. In gonococcal arthritis, tenosynovitis is frequently encountered, especially about the ankles and wrists, and incision will often reveal a purulent exudate in the tendon sheaths. In gout, the deposition of extra-articular deposits of sodium urate has long been recognized. In chronic gout, tophi composed of uric acid are much more apt to be extra-articular than in the joint or synovial membrane proper. One encounters these deposits in the periarticular tissue, in the various bursae—particularly of the elbow and wrist—in the cartilage of the ear and in the subcutaneous tissues. The tendons of the fingers, wrists and toes are very apt to be the site of tophi. Gouty tophi have actually been found in the mitral valve and in cardiac muscle.

Of the various forms of nonarticular rheumatic disease which occur independently of joint lesions, fibrositis and bursitis are the most important and the most prevalent. In spite of the skepticism which has prevailed for years in the United States regarding the actuality of fibrositis, it is now pretty well recognized by rheumatologists the world over that fibrositis is a real disease entity and that

it cannot be ignored in any discussion of rheumatism. Slocumb[2] goes so far as to consider fibrositis the most common form of acute and chronic rheumatism. Copeman[3] has called attention to the very high incidence of fibrositis in the armed forces of Great Britain. Seventy per cent of rheumatic patients admitted to a British hospital were classified as having fibrositis. Hench[4] believes that this very high incidence is due to the fact that many instances of what we in America would call psychogenic rheumatism have been classified by the British as fibrositis.

One of the most typical and demonstrable forms of fibrositis is so-called Dupuytren's contracture in the palm of the hand. Fibrositis is also frequently seen in the neck, the lower back and the gluteal region. In all these locations there is considerable fibrous tissue investing the muscles, and any unusual strain on these areas is apt to bring on an acute attack.

Chronic fibrositis is a more difficult condition to explain. It is here that the condition may be confused with psychogenic rheumatism. Rheumatologists are agreed that chronic fibrositis may be profoundly affected by the emotions and, indeed, that the emotions may act as the precipitating factor. In recent years several writers have described the so-called "trigger areas" in fibrositis. These so-called "myalgic spots" are small, tender areas which may give rise not only to local tenderness but also to large referred areas of secondary pain. Copeman[3] believes that the "myalgic spots" often arise in the course of acute infections, particularly in influenza. The so-called "frozen shoulder" is often due to fibrositis of one of the adjacent tendons, and should be differentiated from calcific deposits in the subacromial bursa. Pain and stiffness are quite marked and the patient often has subjective symptoms of numbness and tingling in the fingers of the affected arm.

Finally, one must not forget lumbar and gluteal fibrositis, which are common enough but which must be differentiated from other causes of low back pain, particularly herniation of a lumbar disk. Not infrequently the fibrositis of the back or buttock is associated with panniculitis.

The treatment of these various forms of fibrositis is still far from satisfactory. One thinks first of physiotherapy in its various forms, and it must be stressed that in fibrositis, physiotherapy has one of its most successful fields. Deep x-ray therapy may be of aid where physiotherapy has been unsuccessful. In the opinion of many, hydrotherapy and massage are the most useful forms of physiotherapy in the treatment of these conditions. In view of Copeman's studies, one should always think of a latent infection and the possible necessity for drainage of some focus, such as infected antrums or root abscesses. A substratum of psychic trauma is so frequent in this condition that psychotherapy will also be an important part of the treatment used.

RUSSELL L. CECIL

REFERENCES

1. Steiner, G., Freund, H. A., Leichtentritt, B. and Maun, M. E.: Lesions of skeletal muscles in rheumatoid arthritis. Am. J. Path. 22:103, 1946.
2. Slocumb, C. H.: Clinics 2:169, 1943.
3. Copeman, W. S. C.: Brit. M. J. 2:263, 1943.
4. Hench, P. S., et al.: Ann. Int. Med. 10:754, 1936.

WHAT ABOUT CHLOROPHYLL?

THUS far the available evidence in behalf of chlorophyll and chlorophyll preparations, examined critically, seems to indicate that under some conditions the substance may have deodorant properties, and that it may or may not stimulate wound healing. Chlorophyll is green, and a veritable rash of green cosmetic and medicinal products has broken out over the nation including toothpastes, antiperspirants, deodorants used internally and externally, shampoos, mouth washes, lozenges and dog foods. Some wisecracker has pointed out that the goat eats many pounds of chlorophyll during its lifetime. When I was a boy we had a riddle which went like this: "I have a goat at home that doesn't have a nose." "How does he smell?" "Terrible!" The celebrated Samuel Johnson was seated at dinner next to a beautiful lady. She said: "Mr. Johnson, you smell." "No, madam," he comment-

ed, "you smell; I stink." All of which means that people dislike disagreeable—including body—odors, and are apparently willing to spend millions of dollars to avoid them and to get rid of them.

Good Housekeeping made some simple tests. The editor reports in a recent issue that breath smelled better after use of a chlorophyll-containing toothpaste, but the investigator was unable to determine whether this was due to chlorophyll or to the removal of debris around the teeth. Fifty women took the tablets for a week, meanwhile using no underarm deodorant. "The pills," says the report, "did not work." The tests were limited. Nevertheless *Good Housekeeping* says: "Because of label statements or advertising claims checked in our laboratory and in practical use tests, we have not been able to accept a single cosmetic making specific or implied claims for chlorophyll beyond its uses as a coloring material."

Most of the large producers of toothpastes have brought out chlorophyll-containing products but they are still selling the old ones as well. The scope of use of the products at this time indicates that people will soon find out whether or not they are getting the results they seek. The Food and Drug Administration could establish the facts much more quickly with a few simple experiments. It's their problem!

MORRIS FISHBEIN

THE PEOPLE AND THE LAWYERS

In a Class Day address to the graduating class in law at Northwestern University in June, Judge Julius J. Hoffman had a word to say on public opinion of lawyers. A recent poll showed that 60 per cent of people questioned did not like lawyers, 56 per cent thought their fees were excessive, 51 per cent had never used the services of a lawyer, and 79 per cent were dubious about the lawyers' honesty.

The Chicago Bar Association in the light of this poll decided to establish a public relations office. Judge Hoffman made this comment: "You, in your future practice, can do something much more fundamental. The best public relations do not emanate from press releases but from the behavior of individuals. The best public relations man for the legal profession is the honest, intelligent, civic minded lawyer. It is not enough for lawyers to publicize a code of ethics if they violate it or condone violations. It is not enough to cite examples of benefactions and public service if the legal profession does not at the same time make the greatest effort to eradicate abuses and public disservice."

No better text on public relations in a profession was ever written in either the field of law or of medicine. When a profession deserves to be loved by those whom it serves, it gets all the love it can possibly use.

MORRIS FISHBEIN

COUGH-SUPPRESSING DRUGS

A most interesting contribution to modern pharmacology is that of B. R. Hillis[1] of the Department of Materia Medica and Therapeutics in the University of Glasgow who has recently undertaken a study of cough-suppressing drugs. People cough in order to get rid of irritating substances in the respiratory tract. A brief spell of forceful coughing may be desirable whereas repeated coughing may damage the mucosa of the upper respiratory tract and create areas of diminished resistance, new infection and a secondary cause of uncontrollable coughing. Persistent coughing at night results in physical exhaustion due to loss of sleep and to other difficulties.

Obviously, sound therapy would demand eradication of the underlying cause of a cough. Symptomatic treatment is usually tried, however, to produce relief. Expectorants are used to increase the flow of secretion and perhaps to wash away irritants but evidence is lacking that they actually do this. Sometimes lozenges of one type or another increase the flow of saliva and lubricate the irritated area. Most physicians depend, however, on opiates and on analgesics for depressing the cough center in the medulla.

These depressants suffer as a group from undesirable side effects, including drowsiness, nausea and constipation.

The study was based on the development of a method for producing artificially coughs of predictable severity indistinguishable from a natural cough. All the investigations were made on a volunteer, a man, aged 42, who had developed the ability to resist a definite stimulus, namely, the insertion of a sprayer over the root of the tongue into the lower pharynx. A small quantity of fluid sufficiently irritating to precipitate coughing was sprayed into the larynx. A variety of substances, including water, peppermint water and trichlorethylene, were used. Then the investigators determined the number of coughs before and after injection of the drugs. Ether gave a 100 per cent cough response when blown into the respiratory tract and peppermint water was not a sufficiently strong stimulus to produce 100 per cent cough response. Altogether 102 experiments were done. The experiments lasted over a year and the author took into account the psychologic effect by comparing the use of cough-suppressant drugs and mixtures with various placebos.

The psychologic factor was found to be important. Codeine gave results which were much less predictable and consistent when given by mouth than when injected subcutaneously. Morphine also gave variable results.

The investigator concludes that morphine, diamorphine and AMIDON® are potent cough suppressants. Evidence was not obtained that the action of codeine is any greater than can be explained by the factor of suggestion.

MORRIS FISHBEIN

1. Hillis, B. R.: The assessment of cough-suppressing drugs. The Lancet, June 21, 1952, page 1230.

FIRST AID AT THE FIGHTS

ON Wednesday and Friday nights people who view prize fights on television are getting some of the worst lessons in first aid that have ever been seen. Under the sponsorship of the State Athletic Commission of New York a medical symposium was held recently at the Astor Hotel. Among those participating were Dr. Edward Dunlap, assistant clinical professor of surgery at Cornell University, Dr. Richard Stark, assistant attending surgeon, New York Hospital, and Dr. Charles G. Child, attending surgeon, New York Hospital. Those who have watched the fights on television have observed what handlers and even attendant physicians do when a boxer gets a cut over the eye. The wound is rubbed with a filthy towel, or some carpenter's glue is used to seal the edges; styptic may be applied, or collodion. One report said that enough ADRENALIN® has been rubbed into a wound in several instances to affect pulse, blood pressure and respiration. The wounds may become infected; many fighters display huge scars in areas where wounds, if promptly and properly treated, would be practically invisible.

One expert suggested that oxygen be administered immediately after a knockout to prevent permanent injuries to the brain. Another said that the collapse of the famous Sugar Ray Robinson during a recent fight in New York on a hot night under the klieg lights was due simply to the fact that he took no water during the day preceding the fight nor during the fight itself. The doctor asserts that a few swallows of water during the fight would have prevented the collapse. Anyone who has taken the Red Cross courses in first aid knows the simple facts that are here emphasized in relation to first aid for wounds or for heat exhaustion.

Deaths and permanent injuries following boxing and prize fighting are now sufficiently frequent to make the subject worthy of more serious consideration than has been given to it in the past. The New York authorities, under the leadership of Dr. Marvin A. Stevens, chairman of the medical advisory board of the New York State Commission, have made a beginning. Athletic commissions throughout the nation might well make a few regulations on first aid and teach the handlers a few of the simple measures that every Boy Scout knows.

MORRIS FISHBEIN

MEN OF *Medicine*

Yellow Fever Hits the Jackpot

It was a brilliant gathering that assembled in the Caroline Institute of Medicine on December 10, 1951, to watch King Gustaf distribute the prizes. Standing beside the king was Queen Louise, happy and excited because this was her first public appearance after a long hospitalization. The queen listened intently as Professor Lofstedt referred to the man approaching King Gustaf as a "real benefactor of humanity." She watched with anticipation as a shy, slight, dark-complexioned man came forward to receive a diploma, a huge gold medal and a check for $32,000.

This was Dr. Max Theiler, "conqueror of yellow fever," a member of the International Health Division of the Rockefeller Foundation and the 1951 winner of the Nobel Prize in Physiology and Medicine.

According to the provisions of the will of Alfred Nobel, the peace-loving scientist whose millions from the discovery and manufacture of nitroglycerin had provided the money for Nobel prizes, the recipients must have accomplished more than all others in their special fields to further the welfare of mankind during the past 12 months. But to the members of the assemblage that day in Stockholm and to others familiar with the facts, the award being bestowed on Dr. Theiler was of even greater significance.

The occasion marked the fiftieth anniversary of the presentation of the first Nobel prize. So, to do special honor to the day, those chosen to receive awards were, as nearly as possible, the persons throughout the world whose contributions had been the greatest during the last half century.

Conqueror is not the word one would expect to use in describing such a modest, unassuming individual as Dr. Theiler, a man who has steadfastly refused to take credit for any accomplishment. He insists that all credit belongs to the Rockefeller Foundation and to his associates, especially to the late Dr. Wray Lloyd and to Dr. Hugh M. Smith. Dr. Theiler was amazed to hear that he was the recipient of the Nobel prize for 1951. When he was told that the prize amounted to more than $32,000, he said incredulously, "Well, it looks as though the yellow fever got me the jackpot."

When newspaper reporters asked him what he would do with the money, he said that he guessed he would buy a case of Scotch. He would also go to see the Brooklyn Dodgers play a few games, explaining that he was a Dodger fan "because the Dodgers have never won a World Series and I'm for the underdog." Dr. Theiler played cricket while attending English schools but he is admittedly far more keen about baseball.

Dr. Theiler is an exceedingly human individual despite his more than 25 years dedicated to continuous, laborious research activities. But he is a prodigious worker, usually arising at 4 A.M. to start his work for the day. Sometimes he arises at 3, and arises as late as 5 "only if I oversleep."

When his face is in repose, he looks sad and at times appears to be rather forbidding. But his flashing smile is completely disarming and he smiles frequently. His hearty laugh rings out beyond the walls of his laboratory, usually in appreciation of a witty re-

MAX THEILER, M.D.

mark made by an associate. He relaxes by reading books on history and philosophy but he is not at all averse to reading Sherlock Holmes and other murder mysteries provided they are well written.

Dr. Theiler was born on January 30, 1899, at Pretoria. His parents were Swiss and his father, the late Sir Arnold Theiler, was the best known scientist in all of South Africa. In fact, it is doubtful if Max Theiler would have come to the United States had his father been a man of less note in the world of science. As matters stood, however, the son felt that there was hardly room for two Theiler scientists in South Africa. Should he be so fortunate as to accomplish anything, he feared that his accomplishments would be discounted or, if accepted, they would be accepted merely as the contributions of the son of Sir Arnold. Stubbornly determined to be on his own and let his achievements rise or fall on their own value, Max Theiler was delighted to accept a post at Harvard University shortly after graduating from the London School of Tropical Medicine and Hygiene.

This was in 1922, the same year Dr. Theiler became a member of the Royal College of Surgeons and a licentiate of the Royal College of Physicians. Earlier studies had included attendance at the Medical School of the University of Capetown and at various schools in Switzerland.

While pursuing research studies on yellow fever at Harvard University, Dr. Theiler met and married Lillian Graham of Boston. The Theilers have one child, a 13 year old daughter named Elizabeth, who went to Stockholm with her father and was present when he received the Nobel prize.

One cannot appreciate the true significance of that moment in Stockholm and of Dr. Theiler's contributions without leafing back into the pages of medical history.

Yellow fever was unknown to the ancients but became the scourge of armies, navies and explorers in the seventeenth century. From that time and for 200 years, yellow fever was one of the most dreaded of all diseases. Both medical and lay records attest to the general fear with which the fever was regarded. Yellow fever, rather than man power and tactical superiority, had been the deciding factor in many military engagements. Admiral Edward Vernon, better known as "Old Grog," lost 8,431 of 12,000 men at Cartagena, Colombia, from yellow fever in 1741 while trying to take the West Indies from the Spanish. Other leaders lost similarly large numbers.

Worse yet, yellow fever had a way of traveling. Philadelphia had 20 serious epidemics. New York City, Boston, Charleston and a score of other cities had suffered terrible epidemics, and what had happened once could happen again. With the opening of the Panama Canal yellow fever became an ever present threat to the peoples of the Far East and other parts of the world. Yellow fever, in fact, remained a sinister menace up until and during a portion of World War II.

Dr. Carlos Finlay of Havana, Cuba, had long since voiced his belief that the vector of yellow fever was the mosquito. Major Walter Reed had demonstrated that such was the case. Reed and others had also demonstrated that while the causative factor in yellow fever is ultramicroscopic and filtrable, regions may be made safe from fever ravages through adequate mosquito control.

But knowledge of how to control yellow fever was still fragmentary. The fever continued to rage in Mexico, Central and South America and in Africa. Furthermore, the confines of territorial boundaries were less and less important and global warfare was a matter of everyday conversation. Altogether, the time had passed when it was practical to attempt to control diseases by making regions safe for people. Who could foretell what regions men would be called upon to enter on short notice? Often there would not be time to institute adequate sanitary measures for man's protection. In view of these things, immunization had become the only practical solution.

Had immunization not been necessary for the armies and navies of the world, it would have been necessary for the scientists. Many had become medical martyrs, sacrificed in their efforts to unravel the mysteries of yellow fever. Six members of the Rockefeller

Foundation staff alone had contracted the fever and died while seeking to learn more about the disease.

Notable among these martyrs was the Japanese-American scientist Hideyo Noguchi, a member of the Foundation's Yellow Fever Commission sent to study the disease in South America. The Commission discovered that the only endemic center in South America was in Guayaquil, Ecuador, and attempted to eradicate the fever in that region. These efforts were delayed by World War I. But Noguchi, by studying the mosquitoes around Guayaquil, discovered a *Leptospira* that produced yellow fever-like lesions in guinea pigs. When Noguchi later obtained the same organism during yellow fever epidemics in Mexico, Peru and Brazil, he decided that he had discovered the cause of yellow fever and set out to develop a vaccine.

Dr. Theiler, then a young research scientist working with Dr. A. W. Sellards, the associate professor of tropical diseases at Harvard University, was among the few who were not convinced by Noguchi's evidence. Theiler believed that Noguchi had failed to discover the organism responsible for yellow fever. And time proved that such was the case. Later developments demonstrated that Noguchi instead had uncovered the organism responsible for spirochetal jaundice. While spirochetal jaundice resembles yellow fever clinically, as the name indicates, spirochetal jaundice is caused by a spirochete. Yellow fever is caused by a virus.

Believing that the yellow fever organism was yet to be discovered, Dr. Theiler was exceedingly interested when the Rockefeller Foundation dispatched a group of scientists, known as the West African Yellow Fever Commission, to determine whether the disease known as yellow fever in South America was the same as that called yellow fever in Africa. Dr. Theiler was further interested when the members of the Commission failed to find any evidence that the *Leptospira* was involved in any way with yellow fever as it existed in Africa, although the scientists did produce evidence that the disease has a common etiologic factor.

The activities of the West African Commission also made available for the first time the knowledge of jungle yellow fever and its epidemiology. Medical science was now faced with the problem of yellow fever virus lurking in the forests, to remain a constant threat to adjacent urban centers, and through those centers to threaten the world. More clearly than ever, immunization was established as the only practical answer to protect mankind against yellow fever.

During June 1927 Dr. A. F. Mahaffy, a member of the Commission, was successful in transmitting the yellow fever factor to a rhesus monkey. This was a great step forward as it marked the first time the fever had been transmitted to an animal under laboratory conditions. Previous studies on the fever had been conducted on human volunteers.

Following the work of the West African Commission, Dr. Sellards went to Dakar and there, in West Africa, confirmed the findings of the Commission. Thereupon Dr. Theiler obtained through Dr. Sellards a sample of the material successfully used in transmitting yellow fever to monkeys.

Dr. Theiler was impatient to go even further but was hampered because of the scarcity of laboratory animals. Rhesus monkeys were expensive and not easily obtained. Believing that many animals were required to obtain reliable information, Dr. Theiler devised the brilliant expedient of transmitting yellow fever to common white mice by inoculating them through the brain. Other scientists had tried to use mice but had discarded the animals as not being susceptible to yellow fever and thus of no importance in trying to learn about the disease. But by using imagination and injecting the mice in the brain, Dr. Theiler found that these animals suited the purposes admirably.

In 1929, during this phase of Dr. Theiler's experiments, he himself developed yellow fever. Fortunately he suffered a light case and was soon able to go ahead with further research.

Transmitting yellow fever virus from mouse to mouse, he discovered that the virus had fatal effects after the sixth day. As soon as a

mouse was stricken, the brain was removed and the material from the infected brain was used to inoculate other mice. While the injections were fatal to other mice, the injections were less effective in monkeys. After 200 passages of the injection material from mouse to mouse, a virus resulted which gave monkeys immunity to yellow fever. The virus, ordinarily fatal to the monkeys, lost its effect when the animal was protected by a dose of virus prepared from a yellow fever-stricken rodent.

In 1930 Dr. Theiler was asked to join the staff at the Rockefeller Foundation. It was hoped that through more ample research facilities this scientist might be able to develop a dependable vaccine that could be used safely on great numbers of people.

Although Dr. Sellards in North Africa and Dr. W. A. Sawyer in America had made limited use of the mouse-passage virus to inoculate human beings, Dr. Theiler did not believe that the mouse-derived vaccine then available was altogether safe. On the other hand, the results already obtained made him feel reasonably certain that he was on the right track. He believed that the main problem was to develop a more attenuated virus. The virus to be released for use in humans must protect people without in any sense endangering health.

At this point Dr. Theiler started a large series of tissue-culture experiments. One type of tissue after another was tried and discarded. At long last the answer was found in the tissue of the chick embryo, and after hundreds of trials and many errors a vaccine was perfected that proved both harmless and protective for persons subjected to yellow fever virus. Cautiously, Dr. Theiler used the vaccine on a few subjects. Between May 13 and June 29, 1931, 10 persons were inoculated with the fresh, sterile, immune virus. Soon the research workers at the Rockefeller Foundation breathed a great sigh of relief. They knew that now, for the first time, they were safe from yellow fever.

As the success of the immunization method was further and further demonstrated, larger and larger groups of people received its benefits. More than 28 million doses of the vaccine were prepared by the Rockefeller Foundation between 1940 and 1947. The doses were distributed without charge to the Allied governments for distribution to troops and other personnel assigned to duty in the tropics. Millions of additional doses were manufactured by industrial laboratories following the Theiler method.

More than 50 million persons have now been vaccinated against yellow fever. The successful outcome means that Dr. Max Theiler has performed a scientific feat, bearing the same relation to the control of yellow fever that the smallpox vaccine developed by Edward Jenner holds in the control of smallpox. The yellow fever vaccine, known as 17D, has permitted countless white men to penetrate into hitherto closed parts of the tropics, notably in South America and in Africa.

But Dr. Theiler, now director of laboratories for the Division of Medicine and Public Health at the Rockefeller Foundation, says that a vaccine to immunize people against yellow fever is only the beginning. What was accomplished in the case of yellow fever must be accomplished to protect people against other insect-borne virus diseases of the world.

While studying yellow fever, members of the field staff of the Foundation, together with Colombian, Brazilian and British scientists working under Foundation auspices, discovered 12 other diseases which, like yellow fever, are essentially diseases of wild animals. These diseases, again like yellow fever, may escape from the jungle, be transmitted and prove deadly to man. They too must be tracked down, says Dr. Theiler. Their importance in the human scheme must be determined and, where indicated, the means must be provided to protect mankind against these thus far unknown foes.

Such are the accomplishments for the future in giving man adequate armor to withstand his environment.

MIRIAM ZELLER GROSS

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TYPICAL PATCH TEST

Over 400 infants and children from 2 weeks to 6 years of age acted as test subjects to check the incidence of sensitivity to orange juice. After 2 to 12 months' observation,* "no disturbance of bowel function (diarrhea or constipation) that could be attributed to the orange juice" was found. Also, the occurrence of regurgitation and rashes was "minimal". In the rare instances of sensitivity, care exercised by gentle reaming of juice (or the use of frozen concentrate) to avoid contamination with peel oil usually obviates the difficulty.

**J. Pediat. 39:325, 1951*

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants.

• RELATION OF ADOPTION TO FERTILITY

Question: People seem to believe that a sterile couple often demonstrates fertility after adopting a baby. Have there been any sound statistical studies of this question? Is it possible that emotional reactions may so affect the endocrine physiology as to stimulate increased efficiency of the procreative mechanism?

M.D.—Washington

ANSWER: I do not know of any sound statistical studies that have been made on this question of the importance of adopting a baby for the relief of sterility. I have talked with one of the consultants here who has done a good deal of work on the subject and he does not know of any sound statistical studies concerning this question. We have always felt that it is possible that emotional reactions affecting the husband or wife may so affect the endocrine physiology as to stimulate increased efficiency of the procreative organism. I think it would be well worth while for studies to be made of this question.

ROBERT D. MUSSEY

• TREATMENT OF IMPETIGO

Question: What is the simplest treatment for impetigo?

M.D.—Illinois

ANSWER: The simplest treatment for impetigo is to wash the areas thoroughly with soap and water three times daily, removing any crusts. One of the newer antibiotics—polymyxin, neomycin, bacitracin, etc.—is then applied. The sensitizing antibiotics—penicillin, streptomycin, etc.—should not be used, since a superimposed contact dermatitis might ensue.

BEDFORD SHELMIRE

• SIDE EFFECTS OF NEW TB DRUGS

Question: What serious side effects, if any, have researchers found in employing the new wonder drugs in the treatment of tuberculosis?

M.D.—Ohio

ANSWER: Toxic reactions which have been reported are intractable asthma, persistent hypotension and increased susceptibility to the effects of other drugs (particularly epinephrine, ephedrine, atropine and DEMEROL®). Minor untoward effects which have been reported are hyperreflexia, constipation, postural hypotension and dizziness, difficulty in starting micturition, eosinophilia, and the appearance of casts, albumin and reducing substances in the urine.

• SYMPTOMS OF IODISM

Question: I have a 65 year old white male patient who has bronchial asthma and emphysema. He recently had plus to 2 plus dependent edema in the lower extremities with "arthritis" or stiffness in his knee and finger joints. He was on potassium iodide and had some of the symptoms and signs of iodism, including profuse discharge from the nose and sinuses, some congestion (moist rales) and ronchi, and pain beneath the corner or angle of the jaw which he described as sore throat. He had a tachycardia of 110 and had taken epinephrine and NEOSYNEPHRINE® from a nebulizer. He has an inverted T wave in CF_4. I gave him digitalizing doses of DIGITALINE NATIVELLE® and took him off the iodides. I wish to know if iodides can be in this differential diagnosis, as I have given him digitaline nativelle once before without edema or

(Continued on page A-28)

98% CURE RATE
in Trichomonas Vaginitis

According to a recent clinical study*, Vagisol Suppositabs —tablet-shaped vaginal suppositories—administered twice daily produced a cure of trichomonas vaginitis in 98 of 100 patients under treatment. In this series, 72 patients were cured in 18 days, 22 in 36 days, and 4 in 54 days. Although all 98 patients were asymptomatic after 2.15 mean patient days of treatment, Vagisol was continued until cultures were repeatedly negative. It was found that a negative wet smear could be misleading, since in many patients a positive culture was found after the wet mount became negative. Thus the hazard of mistaking a temporary remission for a real cure was prevented, and the clinical efficacy of Vagisol was clearly demonstrated.

The remarkable cure rate achieved with Vagisol is due to the potent antibacterial and antiparasitic action of phenylmercuric acetate and tyrothricin, the digestive action of papain, and the surface action of sodium lauryl sulfate. Vagisol also contains lactose and succinic acid to help restore the normal acid pH of the vagina and thereby the regrowth of the Doederlein bacillus.

*Submitted for publication.

SMITH-DORSEY • Lincoln, Nebraska
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Vagisol Suppositabs are odorless, nonstaining, and nonirritating. Each Vagisol Suppositab contains:

Phenylmercuric Acetate	3.0 mg
Tyrothricin, N.F.	0.5 mg.
Succinic Acid	12.5 mg.
Sodium Lauryl Sulfate	3.0 mg.
Papain	25.0 mg.
Lactose	q.s.

Supplied in bottles of 36.

VAGISOL
SUPPOSITABS
A *Dorsey* PREPARATION

joint symptoms and without change in heart rate or dyspnea.

The question is: Does or can iodide cause swelling of the lower extremities with stiffness of finger joints and knee joints?

M.D.—Georgia

ANSWER: The articular or perhaps periarticular reaction described can occur as a part of the manifestations of iodism. It would be expected, however, that the reactions would subside when use of the iodides is discontinued and after these agents have been eliminated from the body.

• SURGERY FOR RICKETS

Question: The parents of an 18 month old child have consulted me relative to her obvious rickets and bowed legs. She has received vitamin D and the x-rays indicate healing, but the parents fear that the bowing of the legs is permanent. If surgery is the answer, when should it be done? Is there any chance of correction without surgery? I have heard that surgery should never be done unless the rickets has completely healed.

M.D.—Wisconsin

ANSWER: I would advise against surgery in a child with rickets unless the bowing of the legs is unusually extreme. After healing has taken place and growth proceeds, there will be a very considerable amount of return to the normal pattern of development by the bones unless there is some complication such as chondrodystrophy. At any rate, I would want to have the rickets cured before subjecting the child to any surgery, because the legs tend to straighten spontaneously.

IRVINE MCQUARRIE

• SPREAD OF CANCER

Question: What are the best technics for biopsy to insure preservation of surrounding tissue and to avoid danger of spread of cancer? Are there any reports of cases in which cancer has spread extensively following use of this diagnostic procedure?

M.D.—Maine

ANSWER: The technics used most often here in obtaining biopsy specimens are (1) the punch or needle biopsy, (2) the use of the biting forceps and (3) direct biopsy using the knife. All our cases are routinely biopsied for two main reasons: (1) to determine whether the lesion in question is malignant or benign, and (2) if malignant, to determine the type or tissue diagnosis. We feel both these reasons to be of such importance to us and the patient in planning the program of treatment that any remote possibility of causing a spread by biopsy is far overshadowed.

We have no reports of any cases where biopsy has caused extensive spread. It should, however, be definitely understood that a biopsy is just one step in the program to set up treatment and not a diagnostic end in itself. In other words, a biopsy should not be done unless a planned treatment program can be started immediately or within a few days. We do not favor doing a biopsy and then having the patient appear for treatment weeks later.

May I suggest two references that may be of interest to you:

1. Mann, M. D. and Dunning, W. F.: Is the biopsy of neoplasms dangerous? Surg., Gynec. & Obst. 82:567 (May) 1946.

2. Does biopsy spread cancer? Cancer Bull. 1:64 (July, August) 1949.

E. C. WHITE

• AMEBIASIS THERAPY

TO THE EDITOR:

The answer to the question on "Amebiasis Therapy" (page A-28, June 1952) seems to me inadequate. (a) Chronic amebiasis as we know it in the United States is more apt to be accompanied by constipation than by diarrhea. (b) Contrary to the implication in this answer, essentially all amebiasis due to *Endamoeba histolytica* leading to invasion of the wall of the large bowel is accompanied within a few weeks to a few months by enlargement of the liver. (c) There is a very real question at this date as to the curative value of AUREOMYCIN® and terramycin in the treatment of amebiasis. Do these medical agents alter and diminish the food supply of the *E. histolytica* only, or are they directly and finally amebacidal? In the writer's opinion it will take many a year to decide this question accurately.

Very truly yours,

L. M. BOYERS, M.D.

Berkeley, California

When it's "Lights Out"... Instead of "Nights Out"

It isn't that she's never *asked* to go out. But she's always so *tired* . . .

For these common hypochromic anemias, therapeutic iron is, of course, your first consideration. Then don't you feel that other deficiencies—which are likely to attend secondary and nutritional anemias—should be treated concomitantly?

First and foremost, IBEROL is *iron*. Just three tablets t.i.d. supply the standard therapeutic dose of elemental iron. But, in addition, IBEROL furnishes generous amounts of vitamin C, folic acid, B_{12}—and other B complex vitamins—plus standardized stomach-liver digest . . . all in a compact, sugar-coated tablet that completely masks all iron and liver traces.

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THREE IBEROL TABLETS: the average daily therapeutic dose for adults, supply:

Ferrous Sulfate (representing 210 mg. elemental iron, the active ingredient for the increase of hemoglobin in the treatment of iron-deficiency anemia)	1.05 Gm.
Plus these nutritional constituents:	
Vitamin B_{12}	30 mcg.
Folic Acid	3.6 mg.
Stomach-Liver Digest	1.5 Gm.
Thiamine Mononitrate (6 times MDR*)	6 mg.
Riboflavin (3 times MDR*)	6 mg.
Nicotinamide (2 times RDA†)	30 mg.
Pyridoxine Hydrochloride	3 mg.
Pantothenic Acid	6 mg.
Ascorbic Acid (5 times MDR*)	150 mg.

*MDR—Minimum Daily Requirement
†RDA—Recommended Daily Dietary Allowance

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THE MEDICAL Bookman

► MODERN TRENDS IN GASTRO-ENTEROLOGY

Edited by F. Avery Jones, M.D., Central Middlesex Hospital, London, with more than 40 contributors. 831 pages with 275 figures. 1952. Paul B. Hoeber, Inc., New York. $20.00.

One of the "Modern Trend" series published by Hoeber, this text does not cover every disease, disorder or phase of gastroenterology, but apparently intends to present recent English developments, ideas and methods in the field. With full and complete knowledge of current facts and practices, the British interpretation of some of the gastroenterologic data is often, and refreshingly, at variance with American or Continental opinion.

Concerning gastritis, the English do not recognize hypertrophic gastritis, but only erosive gastritis, atrophic gastritis and "the gastric lesion of pernicious anemia." Magnus differs from Hurst in not believing that gastritis is the anlage of cancer. Magnus states that the condition of the stomach with cancer is no different from that of the nonmalignant stomach.

The Australians, Doig and Wood, from results of their blind biopsies, are inclined to agree with their British confreres. Doig and Wood have established to their satisfaction a direct relation between the state of the mucosa and the acidity of the gastric secretion; for instance, atrophy and achlorhydria.

The aspects of fat metabolism which have gastroenterologic implications are simplified by Frazer and Cooke. They remark that the distinction between sprue, nontropical sprue, idiopathic steatorrhea and regional ileitis or jejunitis is not always simply or easily made.

The important sequelae of gastrectomy are described and explained by Cappler. Recognizing the several possible individual and combined consequential patterns, this section is headed, in typical British fashion, "After Gastrectomy." Cappler recommends adequate support of the gastric and afferent loop in doing gastrectomy to prevent the postgastrectomy early symptoms. The site of the gastroesophageal junction is secured to the crus of the diaphragm, if necessary, and the afferent loop to the upper edge of the lesser omentum.

An unusual but logical inclusion in a gastroenterologic text is a discussion of anemias of the alimentary tract by L. J. Witts.

Ronald Belsey takes exception to the term "short esophagus" as applied to hiatus hernia. He believes that the designation is seldom justified. Shortening of the esophagus due to fibrotic contraction does occur, but is rare and is associated with some degree of stenosis. That is, apparent shortening is usually acquired and is not congenital. This view conforms to historical and symptomatic data, i.e., distress from hiatus hernia appears after the age of 40.

The point that gastroenterologists, medical or surgical, should do esophagoscopic examinations and not depend on professional endoscopists is properly stressed.

The vascular anatomy of the stomach is demonstrated by Barlow, with many excellent reproductions of his meticulously injected specimens. The tone of the discussion of peptic ulcer is set by Card with the question: Why do people not get ulcers?

Discussion of ulcerative colitis is disappointing. The description of acute diarrhea is illuminating. Joan Taylor calls all such diarrhea food poisoning because the initiating agent is an ingested substance contaminated by bacteria or bacterial toxin. The enterotoxin responsible for symptoms is preformed in the food and therefore acts quickly—that from staphylococci within two hours. Results from straight-out infections are manifest at from 4 to 48 hours and usually at about 20 hours. Infectious diarrhea

(Continued on page A-52)

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lasts from two to five days and is accompanied by fever; toxic diarrhea lasts about one day and the patient is afebrile or has a subnormal temperature. Collapse or shock is more likely with the toxic type. Infectious diarrhea is usually due to *Salmonella* organisms or paratyphoid A, B and C.

Jaundice, hepatitis and cirrhosis are adequately covered, but nothing is said about extrahepatic biliary tract disease.

J. B. C.

► THE UNIPOLAR ELECTROCARDIOGRAM

By Joseph M. Barker, M.D., Cardiologist, Yater Clinic; Associate Professor of Clinical Medicine, Georgetown University School of Medicine, Washington, D.C. 655 pages, illustrated. 1952, Appleton-Century-Crofts, Inc., New York. $12.50.

The author of this volume has succeeded in presenting the subject of unipolar electrocardiography in a comprehensive and simple manner. A section on the arrhythmias is also included.

The book is profusely illustrated with many electrocardiographic tracings depicting not only the more common but also the many unusual electrocardiographic patterns. There is also a large number of diagrammatic figures explaining the subjects in detail.

This fine work should be very useful to the physician and student who want an authentic reference volume for a better understanding of clinical electrocardiography.

T. Z.

► INTERNAL MEDICINE

Originally edited by John H. Musser, M.D., Late Professor of Medicine, Tulane University of Louisiana, School of Medicine, New Orleans, Louisiana. Fifth Edition edited by Michael G. Wohl, M.D., Associate Professor of Medicine, Temple University School of Medicine, Philadelphia. With 80 contributors. 1,563 pages with 236 illustrations and 10 color plates. 1951, Lea & Febiger, Philadelphia. $15.00.

A thoroughly revised text, this book is of special interest to the student and general practitioner. The format is well organized into sections which deal with specific organ systems, thereby permitting easy reference for the busy physician.

Many new sections have been added and the pathologic physiology of disease has been treated at much greater length, to the pleasure of this reviewer, at least.

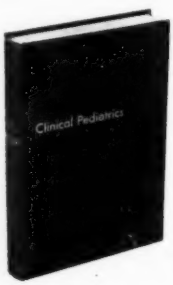
Increasing interest in geriatrics and psychosomatic medicine has found expression in this text and special emphasis has been placed on therapeutic procedures.

While the specialist and graduate student in internal medicine will not find the text a source of reference for all that is new in medicine—and no textbook can fill this requirement—it is an excellent source of reference for the basic concepts of disease as we understand them today.

J. W. L.

► SURVEY OF CLINICAL PEDIATRICS

By Lawrence B. Slobody, M.D., New York Medical College, Flower and Fifth Avenue Hospitals, New York City. 471 pages. 1952, McGraw-Hill Book Company, Inc., New York, Toronto and London. $7.50.



As the jacket states, "Survey of Clinical Pediatrics" is a "focus on the highlights of pediatrics," rather than a textbook in the usual sense. With the exception of a few chapters, this book is written in a modified outline form and without any padding of material. It is divided into 23 chapters with a small but carefully selected bibliography at the end of the text material.

The true and false columns at the end of each chapter should be of particular value to the general practitioner and the graduate medical student preparing for a State Board or Diplomate examination.

The tables and charts representing differential diagnosis are presented in a precise but authentic manner.

M. S.

(Continued on page A-54)

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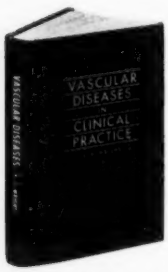
► VASCULAR DISEASES IN CLINICAL PRACTICE

By Irving S. Wright, M.D., Cornell University Medical College, New York City. Ed. 2. 552 pages with 116 figures. 1952, The Year Book Publishers, Inc., Chicago. $8.50.



This is a thorough, interesting and well written coverage of the subject. It is easy to read and adequately illustrated. While the surgical indications are given, the author has refrained from discussing the details of surgical treatment but gives adequate references so that the reader can obtain this information.

There is a wealth of information in this book by which one can answer most questions that may arise on the subject regarding history, signs and symptoms and treatment. Of particular interest is a separate section on the relationship of industrial and medicolegal medicine to peripheral vascular disease and injury.

D. F.

► THE SCALP IN HEALTH AND DISEASE

By Howard T. Behrman, M.D. 566 pages with 312 illustrations. 1952, The C. V. Mosby Company, St. Louis. $12.75.

In his foreword to this most complete available work on the hair, Professor Marion B. Sulzberger says: "The hair is expensive—think of the millions spent on bleaching, tinting and dyeing it; on curling, on waving, or on straightening it out; on cutting it and on shaving it off; on destroying it or on trying to make it grow; on making it lie flat or on making it stand up; to say nothing of the switches, transformations, chignons and other supplements to fill out its deficits."

In an average American family with a mother and two grown daughters, the cost of upkeep of the hair is likely to be far larger than the annual bill for medical care. Apparently Dr. Sulzberger was so convinced of the significance of the hair, particularly in modern life, after reading Dr. Behrman's book that he announces the development of a special "'Clinic for the Scalp and Hair' in one of our hospitals."

Vast amounts of time and energy and study and research have gone into the preparation of this volume. Apparently Dr. Behrman has sought out every available previous contribution including works dealing with immunology, forensic medicine and biochemistry to focus this great amount of information on the hair.

The book is arranged along classic lines beginning with the section on embryology, anatomy and physiology which includes also a most exciting section on anthropology. Next comes a consideration of the care of the normal scalp with some pertinent remarks on brushing, combing, cutting, singeing and shampooing, and on all the various devices and preparations adapted to these purposes. The third chapter is concerned with alopecia and here Dr. Behrman remarks that Hamilton has made the most significant studies of common baldness. These lead to the conclusion that common baldness is developed in families according to certain patterns which are hereditary—thus the name "male pattern alopecia" is given to common baldness. Significant is the contour of the scalp, the heredity, the rate of growth of the brain and various endocrine factors. All of this could, of course, come under the single word "constitution." Dr. Behrman discusses in this connection the various effects of physical agents and of other forces on falling of the hair.

The book proceeds to seborrheic diatheses without, however, any mention of the new selenium preparations which are used in seborrhea. Then comes a section on infections, on scalp disorders of psychogenic origin, and on involvement of the scalp from skin diseases, systemic diseases and tumors. An extensive appendix is a collection of a vast amount of information on the composition of preparations used in the care of the scalp and hair.

The book concludes with an excellent index of some 12 pages. Each chapter is supplemented by an exceedingly well chosen bibliography with the references classified both by alphabetical and subject arrangements. The illustrations in the book are well chosen.

The author of this book has had the advantage of study of the previous volumes on the subject and he has carried such work to a point well beyond anything previously done.

M. F.

(Continued on page A-56)

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Books received will be acknowledged in this department each month. As space permits, books of principal interest to our readers will be reviewed more extensively.

The Treatment of Injuries to the Nervous System. By Donald Munro, M.D., Surgeon-in-Chief, Department of Neurosurgery, The Boston City Hospital. 284 pages with 47 figures. 1952, W. B. Saunders Company, Philadelphia & London. $7.50.

Diseases of the Nervous System in Infancy, Childhood and Adolescence. By Frank R. Ford, M.D., Associate Professor of Neurology, The Johns Hopkins University, Baltimore. Ed. 3. 1,216 pages with 255 illustrations. 1952, Charles C Thomas, Springfield, Illinois. $18.50.

Transactions of the American College of Cardiology. Vol. 1. Edited by Bruno Kisch, M.D. 138 pages, illustrated. 1952, American College of Cardiology, New York.

Metabolic Bone Disease. By I. Snapper, M.D., Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, New York City. 96 pages, illustrated. 1952, Charles C Thomas, Springfield, Illinois. $3.00.

Basic Medical Physiology. By W. B. Youmans, M.D., Professor of Physiology, University of Wisconsin. 1952, The Year Book Publishers, Inc., Chicago. $7.50.

Battle Casualties; Incidence, Mortality, and Logistic Considerations. By Gilbert W. Beebe, Ph.D., Division of Medical Sciences, National Research Council, and Michael E. DeBakey, M.D., Professor of Surgery, Baylor University College of Medicine. 277 pages. 1952, Charles C Thomas, Springfield, Illinois. $10.50.

Jewish Medicine. By Solomon R. Kagan, M.D. 575 pages, illustrated. 1952, Medico-Historical Press, Boston. $10.00.

Applied Physiology. By Samson Wright, M.D., John Astor Professor of Physiology, University of London, Middlesex Hospital Medical School. With the collaboration of Montague Maizels, M.D. Ed. 9. 1,190 pages, illustrated. 1952, Oxford University Press, New York. $9.00.

Disorders in Perception; With Particular Reference to the Phenomena of Extinction and Displacement. By Morris B. Bender, M.D., Professor of Clinical Neurology, New York University College of Medicine. 109 pages. 1952, Charles C Thomas, Springfield, Illinois. $3.00.

Diabetic Glomerulosclerosis; The Specific Renal Disease of Diabetes Mellitus. By Harold Rifkin, M.D., Louis Leiter, M.D. and James Berkman, M.D., College of Physicians and Surgeons, Columbia University, New York. 102 pages, illustrated. 1952, Charles C Thomas, Springfield, Illinois. $3.50.

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